Background Document for Meeting of Advisory Committee for Reproductive Health Drugs
March 4, 2013

NDA 204-516

Paroxetine mesylate capsules 7.5 mg

(Proposed trade name:)

Noven Therapeutics, Inc.

Proposed Indication:

Treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause

Proposed Dosing Regimen:

7.5 mg once daily at bedtime

Prepared by the Division of Reproductive and Urologic Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

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The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought NDA 204-516 to this Advisory Committee in order to gain the Committee's insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the Advisory Committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the Advisory Committee meeting.

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List of Abbreviations and Definitions

AE	Adverse Event
AUC	Area under the curve
BMI	Body mass index
C-CASA	Columbia Classification Algorithm for Suicide Assessment
Cmax	Maximum concentration
CNS	Central nervous system
CSR	Complete Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
DESS	Discontinuation-emergent signs and symptoms
DVT	Deep vein thrombosis
ECG	Electrocardiogram
FDA	Food and Drug Administration
GI	Gastrointestinal
IND	Investigational New Drug Application
IVRS/IWRS	Interactive Voice Response System/Interactive web Response System
LOCF	Last observation carried forward
MAOI	Monoamine oxidase inhibitor
MI	myocardial infarction
MITT	Modified Intent-To-Treat
NDA	New Drug Application
PE	Pulmonary embolism
PGI	Patient Global Impression
PK	Pharmacokinetic
ROC	Receiver Operating Characteristic
SAE	Serious adverse event
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SMQ	Standardized MedDRA Query
SNRI	Serotonin-norepinephrine reuptake inhibitor
SOC	System organ class
SPA	Special protocol assessment
SSRI	Selective serotonin reuptake inhibitor
STS	Suicidality Tracking Scale
US	United States
VMS	Vasomotor symptoms

DRAFT TOPICS FOR DISCUSSION

Committee members are asked to reflect upon the following issues as they review the information provided in this Background Document.

Issues for discussion include the following:

- Based on the Applicant's and FDA's analyses, is there sufficient evidence to conclude that paroxetine mesylate is effective in treating moderate to severe vasomotor symptoms (VMS) associated with menopause?
- Based on the Applicant's and FDA's analyses, is there sufficient evidence to conclude that the change from baseline in VMS frequency is clinically meaningful to women?
- Is the overall risk/benefit profile of paroxetine mesylate acceptable to support approval of this product for the proposed indication?

1. Background

1.1 Objective of Meeting and Overview of Development Program

The purpose of this Advisory Committee meeting is to review and discuss the efficacy, safety and overall risk/benefit profile of paroxetine mesylate capsules, a selective serotonin reuptake inhibitor (SSRI) indicated for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause. This NDA is brought to the Advisory Committee because, if approved, it would potentially be the first and only nonhormonal product approved for treatment of VMS. In addition, while both studies demonstrated a statistically significant reduction on two of the four co-primary efficacy endpoints, VMS frequency at Weeks 4 and 12, the efficacy analysis did not meet the required statistical level of significance for the reduction of VMS severity from baseline to Week 12 in one of the two studies. Further, the one study that evaluated whether the reduction in frequency of VMS was clinically meaningful to women showed clinically meaningful changes only at Week 4 and not at Week 12. Finally, as with any drug, the overall risk/benefit profile of the product for the requested indication must be assessed.

The primary sources of the clinical efficacy and safety data in support of approval of paroxetine mesylate for this indication are two US phase 3 randomized clinical trials (Study N30-003 and Study N30-004, hereafter referred to as Study 003 and Study 004, respectively). Data from a phase 2 proof-of-concept study that also used the to-be-marketed dose and formulation was also considered in the safety database.

1.2 Description of Product

Paroxetine was first marketed commercially in the US in 1992 as paroxetine hydrochloride under the brand name Paxil, which is indicated for major depressive disorder, obsessive compulsive disorder, panic disorder, social anxiety disorder, generalized anxiety disorder and posttraumatic stress disorder.

Paroxetine mesylate has a chemical structure similar to paroxetine hydrochloride, the only difference being the associated salt. Paroxetine mesylate capsules are currently marketed as Pexeva (NDA 21-299, approved in 2003) for the indications of major depressive disorder, obsessive compulsive disorder, panic disorder and generalized anxiety disorder. Dosing ranges from an initial dose of 10 mg to a maximum of 60 mg/day, and vary by indication.

Current Pexeva labeling is included in Appendix 1. Important issues described in labeling include:

- A boxed warning about risk of suicidality (class labeling for antidepressants)
- Serotonin syndrome (class labeling)
- Teratogenicity, particularly cardiovascular malformations, with first trimester exposure
- Precautions relating to a risk of seizures, potential reduction in efficacy of tamoxifen due to irreversible inhibition of CYP2D6, akathisia (psychomotor restlessness), hyponatremia, increased risk of bleeding events, bone fracture, and need for caution in patients with certain concomitant illnesses (e.g., narrow angle glaucoma)

Paroxetine mesylate has not been approved in any country for treatment of VMS.

1.3 Treatment of Vasomotor Symptoms

VMS, or hot flushes/flashes, are symptoms of warmth and sweating that are very common (occurring in up to 75% of women) in the menopausal transition. Moderate VMS is defined as a sensation of heat with sweating that does not disrupt the woman's activities, while severe VMS is defined as a sensation of heat with sweating that causes transient cessation of activities. While VMS can be very bothersome, causing discomfort, embarrassment, and disruption of sleep, it is not a life-threatening condition. VMS may persist up to five years, or even longer in a minority of women, but is ultimately a self-limited condition.

While there are a variety of drug products in different formulations (tablet, transdermal system, vaginal ring) approved for the treatment of menopausal symptoms (including both VMS and symptoms related to vulvar/vaginal atrophy), all contain either estrogen alone or estrogen plus a progestin. The estrogen-only products carry a Boxed Warning about the risk of endometrial cancer in a woman with a uterus who uses unopposed estrogen; this risk is mitigated by addition of a progestin. The estrogen and estrogen/progestin products have a Boxed Warning describing findings from the Women's Health Initiative that reported increased risks of stroke, myocardial infarction (MI; associated only with use of estrogen/progestin), deep vein thrombosis (DVT), pulmonary embolism (PE; associated only with use of estrogen/progestin), invasive breast cancer (associated only with use of estrogen/progestin) and probable dementia in women $\geq$ 65 years old. Both estrogen-alone and estrogen/progestin products are contraindicated in women with known, suspected, or history of breast cancer. Other contraindications include other known or suspected estrogen-dependent neoplasia, active or history of DVT or PE, active or history of arterial thromboembolic disease (such as stroke or MI), known liver dysfunction or disease and known thrombophilic disorders. Therefore, there are significant subgroups of women, particularly those with current or a history of breast cancer, who may be symptomatic during menopause but unable to use the hormonal preparations.

Many other products are used off-label to treat VMS, such as antidepressants (including paroxetine), herbal and soy products; however, rigorous evidence of the safety and efficacy of such treatments is lacking.

Paroxetine mesylate, the focus of this Advisory Committee meeting, if approved, would potentially be the first and only nonhormonal product approved for treatment of VMS.

1.4 Regulatory Guidance for the Development of Paroxetine Mesylate for VMS

The FDA issued a draft guidance for clinical evaluation of hormonal products for menopausal symptoms in 2003 (See Appendix 2), and has generally provided guidance based on this document for both hormonal and nonhormonal products intended to treat VMS. This document states that the VMS indication is to treat "moderate to severe vasomotor symptoms associated with the menopause." Clinical definitions of mild, moderate and severe VMS are provided, with moderate hot flushes defined as "sensation of heat with sweating, able to continue activity" and severe hot flushes defined as "sensation of heat with sweating, causing cessation of activity." Recommended entry criteria include postmenopausal women (defined as 12 months of spontaneous amenorrhea, 6 months of spontaneous amenorrhea with serum FSH > 40 mIU/mL, or six weeks post-surgical bilateral oophorectomy) who have a minimum

of 7-8 moderate to severe hot flushes per day or 50-60 per week at baseline. Four co-primary endpoints are recommended:

- Mean change from baseline in frequency of moderate to severe hot flushes at Week 4
- Mean change from baseline in frequency of moderate to severe hot flushes at Week 12
- Mean change from baseline in severity of moderate to severe hot flushes at Week 4
- Mean change from baseline in severity of moderate to severe hot flushes at Week 12

The primary efficacy analyses are intended to show a clinically and statistically significant reduction of both frequency and severity at Week 4 that is maintained at Week 12. Daily diary entries can be used as the basis of the co-primary endpoints.

Paroxetine mesylate for VMS was developed under IND 76,636, and the FDA and the Applicant had a number of discussions about the drug development program, study protocols and statistical analysis plans. At the April 2007 preIND meeting, the FDA recommended that two adequate and well-controlled phase 3 studies would be needed to support the proposed indication, at least one of which should be conducted in the US. The Applicant agreed to follow the 2003 draft Guidance regarding co-primary endpoints.

In further advice provided in 2008 following review of the protocol for Study 003, the FDA stated that a placebo-corrected reduction from baseline in the number of daily moderate to severe hot flushes of two hot flushes per day would meet the definition of a "clinically significant" reduction. It would not be acceptable to demonstrate statistically significant frequency and severity reductions at Week 4 but not at Week 12. An ANCOVA analysis was acceptable to FDA, but FDA did not agree to a responder analysis of the percent of women who experience moderate to severe hot flushes as a co-primary endpoint, in lieu of the Guidance-defined severity endpoint. FDA also requested the Applicant to evaluate the persistence of treatment benefit to 24 weeks of treatment.

An End-of-Phase 2 meeting was held in September 2010; at this time FDA and the Applicant discussed the demonstration of clinical meaningfulness that would be needed if the placebo-corrected VMS reduction was less than two hot flushes per day. A responder analysis based on a cutoff value identified using an anchoring global subject satisfaction questionnaire was recommended. FDA stated that "a product with a clinically meaningful treatment effect would have a statically significantly greater response rate in the treatment arm than in the placebo arm." Because the first trial was underway at the time of this meeting, the FDA agreed that the Applicant could address the evaluation of clinical meaningfulness using an appropriate anchoring questionnaire in the planned second phase 3 study. The Applicant agreed to evaluate the persistence of benefit to 24 weeks of treatment in one of the phase 3 studies. FDA informed the Applicant that it must conduct a formal evaluation of suicidality in the clinical trials according to current FDA guidelines.

The Applicant submitted a Special Protocol Assessment (SPA) for the Study 003 protocol and FDA issued a No Agreement letter in December 2010. Areas of disagreement included the planned evaluation of whether the treatment effect was clinically meaningful, a proposed key secondary endpoint of "awakening from sleep," and other issued relating to data collection and statistical methods. In a post-SPA meeting in February 2011, FDA stated that it was generally in agreement with revisions made by the Applicant and that a new SPA request should be submitted when the revised protocol was submitted for review. FDA

requested that the cutoff used on the global satisfaction questionnaire dichotomize subjects with much improvement or better vs. a little improvement or worse. An SPA Agreement letter was issued for the Study 003 protocol in May 2011, following review of the revised protocol.

FDA provided further guidance on Study 004 in October 2011, including agreement to the proposed responder analysis to evaluate the persistence of benefit, with classification of subjects who prematurely discontinued as non-responders. An SPA was not requested for the Study 004 protocol.

A pre-NDA meeting was held in May 2012. FDA agreed to pooling safety data from the phase 3 and the phase 2 studies.

2. Clinical Development of Paroxetine Mesylate

2.1 Overview of Product Development

The development program for paroxetine mesylate for the VMS indication consisted of one phase 1 single and multiple dose pharmacokinetic (PK) study, a phase 2 placebo-controlled proof-of-concept study, and two phase 3 randomized, double-blind, placebo-controlled safety and efficacy trials. An overview of the clinical studies is presented in Table 1.

Table 1 Clinical Studies for Paroxetine Mesylate for VMS

Phase/ Study ID	Enrollment/ Centers/ Location/ Started-Completed	Study Design	Subjects Entered/ Subjects Completed	Study Duration
Phase 1 Study N30-005	N=24 healthy, postmenopausal women, ages 45-72 1 US center 7/15/11-8/12/11	Uncontrolled single and 14-day repeat dose pharmacokinetic study Paroxetine mesylate 7.5 mg capsule	Paroxetine mesylate: 24/24	3 week screening, 1 day treatment (followed by 5 non-treatment days), 14 days treatment
Phase 2 Study N30-002	N=102 postmenopausal women, ages 40-67 10 US centers 10/29/08-5/26/09	8-week double blind, placebo controlled Paroxetine mesylate 7.5 mg capsule daily vs. placebo	Paroxetine mesylate: 49*/45 Placebo: 52/51	1 week placebo run-in period 8 week tx period
Phase 3 Study N30-003	N=614 postmenopausal women, ages 40-79 70 US centers 6/6/11-1/3/12	12 week double blind, placebo-controlled Paroxetine mesylate 7.5 mg capsule daily vs. placebo	Paroxetine mesylate: 306/271 Placebo: 308/278	7 day screening, 12-day placebo run-in period, 12 week tx period
Phase 3 Study N30-004	N=570 postmenopausal women, ages 40-74 65 US centers 3/30/10-9/12/11	24-week double-blind, placebo-controlled Paroxetine mesylate 7.5 mg capsule daily vs. placebo	Paroxetine mesylate: 285/235 Placebo: 284**/218	7 day screening, 12-day placebo run-in period, 24 week tx period

***One subject randomized to paroxetine did not receive study drug**
**** One subject randomized to placebo did not receive study drug**
Source: Adapted from Applicant's Listing of Clinical Studies, Module 2.7.6 and Module 5.2

2.2 Overview of Pharmacology and Toxicology

Paroxetine binds to serotonin transporters in the synaptic membrane and inhibits reuptake of serotonin following its release from the nerve terminal. There were no nonclinical studies submitted to support the new indication of treatment of VMS associated with menopause. Because the physiological basis of VMS has not been established, the mechanism of action of paroxetine mesylate in potentially regulating VMS is not known. The Applicant is cross-referencing approved NDA 21-299 (Pexeva) for nonclinical toxicity testing of the drug product.

2.3 Overview of Clinical Pharmacology

The mechanism of action of paroxetine mesylate with respect to treatment of VMS is unknown.

Paroxetine is completed absorbed after oral dosing and bioavailability is not affected by concomitant food intake. In a study of 24 subjects taking paroxetine mesylate 7.5 mg once daily for 19 days, the steady-state maximum plasma concentration of paroxetine (Cmax) was 13.1 ng/mL and the total exposure (AUC) of paroxetine is eight times higher than that observed after a single dose. The excess accumulation is a consequence of the saturation of a major metabolizing enzyme (CYP2D6) of paroxetine at the clinical dose. Paroxetine distributes throughout the body including the central nervous system (CNS), with only 1% remaining in the plasma. Paroxetine is extensively metabolized and the metabolites are considered to be inactive. The mean elimination half-life of paroxetine is about 17 hours after a single 7.5 mg dose. Paroxetine systemic exposure (AUC and Cmax) doubled in patients with hepatic impairment or in patients with creatinine clearance of 30 to 60 mL/min compared to healthy subjects. In patients with creatinine clearance below 30 mL/min, there was a four-fold increase in paroxetine systemic exposure. No dose adjustment is considered necessary for 7.5 mg paroxetine in patients with renal or hepatic impairment considering the relative low dose compared to the approved paroxetine doses.

2.4 Overview of Clinical Studies

The clinical portion of the NDA focuses on review of the two phase 3 studies for efficacy, and includes the phase 2 study as well as the phase 3 studies for safety. Efficacy data from Study N30-002 were not pooled with the phase 3 studies due to differences in the definition of the modified intent-to-treat (MITT) population and because the treatment duration for the phase 2 study was limited to eight weeks.

A total of 1,184 subjects were enrolled in the two phase 3 trials, 591 of whom used paroxetine mesylate. A total of 614 subjects were enrolled in Study 003 (306 on paroxetine mesylate and 308 on placebo) and 570 subjects were enrolled in Study 004 (285 in each arm).

2.5 Basis for Dose Selection

At the End-of-Phase 2 meeting, the Sponsor noted that it had selected the 7.5 mg dose based on published literature showing efficacy for VMS symptoms for 10-25 mg doses of the approved paroxetine mesylate product. There did not appear to be a dose-response in the published literature, so the Sponsor selected a dose lower than that approved for psychiatric indications in order to have a dose that would likely show efficacy while also being safe and well-tolerated.

There were no explorations for dose response in this submission. The only dose studied was the 7.5 mg dosage form.

3. Objectives and Design of Phase 3 Trials

The efficacy of paroxetine mesylate as a treatment for VMS associated with menopause was studied in two phase 3 studies (at a dose of 7.5 mg once daily at bedtime) in 1,174 postmenopausal women who had a mean total frequency of ≥ 56 moderate to severe vasomotor symptoms per week (≥ 7-8 per day on average) for 30 days prior to receiving study drug.

Study 003 was a 12-week clinical trial, with a total of 614 postmenopausal women randomized 1:1 to receive paroxetine mesylate or placebo; this trial also evaluated the clinical meaningfulness of the change from baseline in VMS frequency.

Study 004 was a 24-week clinical trial, with a total of 570 postmenopausal women randomized 1:1 to receive paroxetine mesylate or placebo, and also evaluated the persistence of benefit over 24 weeks of treatment.

3.1 Study Objectives

Primary Objective

The primary objective of the trials was to assess the safety and efficacy of paroxetine mesylate for treatment of VMS associated with menopause.

Secondary Objectives

The Applicant listed a number of secondary objectives; FDA was particularly interested in those that addressed the evaluation of the clinical meaningfulness of the treatment effect on VMS frequency and of the persistence of benefit to 24 weeks of treatment.

3.2 Overall Study Design and Conduct

Both studies were randomized, double-blind, placebo-controlled, multicenter studies in women with either natural or surgical menopause. Both trials were conducted entirely in the US.

3.2.1 Study Schedule and Conduct

The Schedule of Events is displayed in Appendix 3. Following Screening, eligible subjects entered a 12-day single-blind placebo Run-in Period. During the Run-in Period, all subjects were dispensed single-blind placebo capsules (subjects were blinded to capsule content), which they took once daily at bedtime. Subjects were also asked to complete hot flush and sleep diaries each day using the Interactive Voice Response System/Interactive web Response System (IVRS/IWRS), recording the number of hot flushes daily, the severity of each episode of hot flush and total number of awakenings due to hot flushes.

Following completion of the Run-in Period, subjects who were compliant with diary entry and dosing and who continued to meet hot flush eligibility criteria (i.e., having more than 7 to 8 moderate to severe hot flushes per day or 50 to 60 moderate to severe hot flushes per week) were randomized into the Double-blind Treatment Period in a 1:1 ratio to receive either paroxetine mesylate (7.5 mg capsule) or placebo. Study treatment was taken orally once daily at bedtime beginning on Day 1 (day of randomization) and continuing up to Day 84 (Study 003) or Day 168 (Study 004). Subjects continued to fill out the daily hot flush and sleep diaries each day.

Daily Diaries

The phase 2 study and both phase 3 studies used an electronic diary using the IVRS/IWRS for daily entry of hot flush data. This electronic diary was the only source document for the four co-primary endpoints. The diary was available to the subject throughout the day or night. To minimize recall, subjects were encouraged to enter hot flush data as soon as they experienced a hot flush, or at least once daily. Subjects were also provided with definitions of mild, moderate, and severe hot flushes, which conformed to those specified in the VMS Guidance.

3.2.2 Eligibility Criteria

Inclusion criteria specified postmenopausal women with 7-8 daily (or 50-60 weekly) moderate to severe VMS and were identical in the phase 2 and phase 3 studies. Subjects

were to discontinue any psychotropic drugs or hormone therapy prior to starting the study and additional entry criteria specified discontinuation periods for psychotropic drugs and for estrogen alone or estrogen/progestin containing products prior to the Run-in Visit.

Exclusion criteria were generally similar across the phase 2 and phase 3 studies. All phase 2 and 3 studies disallowed enrollment of subjects who were non-responders to previous SSRI or serotonin-norepinephrine reuptake inhibitor (SNRI) treatment for VMS, had evidence of impaired liver or kidney function, or with any clinically significant abnormality noted during screening. Excluded medical conditions in the phase 2 and 3 studies included psychiatric disorders (either lifetime history or more recently prior to screening), hypertension (unless on a stable dose of anti-hypertensive medication), clinically unstable cardiac disease, biliary tract disease, and thyroid disease (unless stable).

Two exclusion criteria were used in only a single study:

- Study 003 excluded subjects taking monoamine oxidase inhibitors (MAOIs), thioridazine, or pimozide (MAOIs were to be discontinued for at least four weeks prior to the Run-in Visit per the inclusion criteria)
- Study 004 excluded subjects with a body mass index (BMI) $\geq$40 kg/m^2.

FDA Comment
Although the risk of suicidal behavior and ideation is a concern for this class of drugs, the entry criteria excluded women with current or historical psychiatric disorders. Thus, the impact of paroxetine mesylate on such women, who may be particularly vulnerable, cannot be assessed in the clinical trials.

In both phase 3 studies, subjects were re-qualified for participation after the 12-day placebo Run-in period.

FDA Comment
FDA agreed to the plan to minimize "placebo responders" by requiring subjects to re-qualify on the basis of VMS frequency and severity after the placebo Run-in period.

3.3 Efficacy Assessments

3.3.1 Analysis Populations

The primary statistical analyses were conducted on the MITT population (efficacy) and Safety population (safety), which were pre-defined by the Applicant as

- MITT population (this was the primary efficacy population): all consented and randomized subjects who had valid baseline hot flush diary data, received at least one dose of their randomized treatment, and had at least one day of on-treatment daily diary data
- Safety population definition: all randomized subjects who received at least one dose of their randomized treatment and had at least one post-treatment safety assessment

Table 2 Summary of Analysis Populations, Phase 3 Studies

Analysis Population	Paroxetine mesylate n (%)	Placebo n (%)	Total n (%)
Study N30-003 (N)	306	308	614
MITT	301 (98.4)	305 (99.0)	606 (98.7)
Safety	301 (98.4)	305 (99.0)	606 (98.7)
Study N30-004 (N)	285	285	570
MITT	284 (99.6)	284 (99.6)	568 (99.6)
Safety	285 (100)	284 (99.6)	569 (99.8)

Source: Complete Study Report (CSR) for Study 003, Table 9 and for Study 004, Table 10

FDA Comments

- **The FDA agreed upon the definition of the MITT population during the drug development discussions.**
- **The numbers of subjects in the MITT and safety populations were very similar to the numbers of subjects randomized, indicating little early loss of subjects.**

3.3.2 Efficacy Endpoints and Analyses

Primary Endpoint

In both studies, the co-primary efficacy variables were:

- Mean change from baseline in average daily frequency of moderate to severe VMS at Week 4
- Mean change from baseline in average daily frequency of moderate to severe VMS at Week 12
- Mean change from baseline in average daily severity score of moderate to severe VMS Week 4
- Mean change from baseline in average daily severity score of moderate to severe VMS at Week 12

The average daily frequency during the treatment period for a specific week was calculated as the total number of moderate to severe hot flushes from self-reported diaries in that week divided by 7. The average daily severity was defined as the mean of daily severity scores over reported days during a specific treatment week, and the daily severity score was calculated as the sum of (2 x the number of moderate hot flushes, plus 3 x the number of severe hot flushes), divided by the total number of moderate and severe hot flushes in that day.

The severity (scoring) of hot flushes was defined as:

- Mild (1): sensation of heat without sweating
- Moderate (2): sensation of heat with sweating, able to continue activity
- Severe (3): sensation of heat with sweating, causing cessation of activity

In the event that a subject entered fewer than four days of diary data in a one week treatment interval, the average daily frequency and severity were imputed by the average of the hot flush diary data over the most recent previous seven days' entries, even if this interval spanned two treatment weeks.

Primary Analysis

For each co-primary endpoint, if the data were normally distributed, a repeated measures analysis with the baseline as a covariate, treatment and week as factors and a random effect component (mixed model) would be used. If the normality assumption was not met, a rank–ANCOVA analysis, i.e., an ANCOVA analysis on rank-transformed data, with ranked baseline value of the endpoint as a covariate and treatment group as a factor would be used for hypothesis testing.

Descriptive statistics were reported for each endpoint. Graphical presentations of the change in frequency and severity from baseline to Week 12 were also provided. The primary analysis relied on observed case data, with no imputation of missing data. For sensitivity assessment, the last observation carried forward (LOCF) method was used to impute the missing data of each co-primary endpoint for the subjects who withdrew prematurely. The FDA statistical reviewer reported the difference between medians as a more appropriate estimate for the treatment effect of paroxetine mesylate relative to placebo in the case of skewed (non-normally distributed) data.

Secondary Endpoints

The Applicant pre-specified a subgroup analysis of women dichotomized on the basis of BMI (< 32 kg/m^2 vs. ≥ 32 kg/m^2).

Clinical Meaningfulness

When lower doses of estrogen products and nonhormonal treatments have been evaluated for the treatment of VMS, the FDA has observed that the magnitude of the treatment effect on VMS frequency is often less than that observed for "standard" dose hormonal therapies. In order to ensure that such treatment effects are still of clinical benefit to women the FDA has requested that an analysis of the "clinical meaningfulness" of the change in VMS frequency be conducted for those products that do not demonstrate a placebo-adjusted reduction in moderate to severe VMS frequency from baseline of at least two hot flushes per day. Although these analyses are typically not specified as primary analyses in the statistical analysis plan, the FDA does consider the results in its evaluation of whether acceptable efficacy has been demonstrated.

In Study 003, the Applicant pre-specified an analysis to evaluate the clinically meaningfulness of the observed treatment effect, using the following steps if the difference between paroxetine mesylate and placebo in the change from baseline in average daily frequency of moderate to severe hot flushes was < 2.

a) First, all MITT subjects in the study, regardless of treatment assignment, were categorized into two groups (i.e., satisfied and unsatisfied) based on a 7-point Patient Global Impression (PGI) questionnaire administered at Weeks 4 and 12 that assessed the subject improvement in VMS. Subjects were considered "satisfied" with their treatment if their response to the question *"Compared to before starting the study medication, how would you describe your hot flushes now?"* was *'Very much better'* (1), *'Much better'* (2) or *'A little better'* (3) and were considered unsatisfied if the response to the same question was *'No change'* (4), *'A little worse'* (5), *'Much worse'* (6) or *'Very much worse'* (7). LOCF was used to handle any missing PGI score for this analysis.

b) The FDA requested that a second analysis be conducted using a different definition of satisfaction. For this analysis, subjects would be considered satisfied with their treatment if their response to the question were *'Very much better'* (1) or *'Much better'* (2). Subjects with responses of *'A little better'* (3) or worse (4-7) were considered unsatisfied. This was the definition the FDA had recommended, as it is more conservative to consider that women who experienced only a "little" improvement might not find this satisfactory, particularly if the drug also had unpleasant side effects.

c) Using this category of satisfied and not satisfied as the dependent variable, a logit model was fit to perform a receiver operating characteristic (ROC) analysis in order to determine the cutoff point for a clinically meaningful reduction in VMS frequency.

d) Based on the cutoff point established above, a responder analysis was performed by categorizing women in the paroxetine mesylate and placebo groups as responders or non-responders. Responders were defined as those subjects who achieve a mean daily hot flush frequency reduction greater than the established cutoff-point and non-responders were defined as those subjects whose mean daily hot flush frequency reduction was less than or equal to the established cutoff-point.

e) A logit model was then used to compare the proportion of responders between the treatment groups adjusting for the baseline number of hot flushes as a covariate in the model.

FDA Comment

This background package will present the analysis above using the FDA-recommended definition of satisfaction.

Persistence of Benefit

In Study 004, a secondary analysis was planned to assess the persistence of efficacy at Week 24 using the following responder analysis. Responders were defined as those subjects who achieved ≥ 50% reduction from baseline in moderate to severe hot flush frequency at Week 24.

Persistence of benefit would be demonstrated by showing a statistically significant difference in the responder rate between the active and the placebo treatment groups. The logit model was used to analyze the proportion of responders, with baseline number of hot flushes as a covariate in the model. In this analysis, subjects who dropped out before Week 24 were considered non-responders, along with those who achieved <50% reduction from baseline.

FDA Comment

The Division agreed to this plan of analysis.

Post Hoc Subgroup Analyses

The FDA conducted routine subgroup analyses on the basis of race (White/Non-White) and menopausal status (surgical vs. natural). In both studies, analysis of each co-primary efficacy endpoint by subgroups was performed using the same rank-ANCOVA model described previously with additional terms for subgroups and treatment by subgroup interaction. The descriptive statistics and estimated median difference between treatment groups were reported for the co-primary efficacy endpoint by subgroups.

4. Efficacy Results

4.1 Enrollment and Disposition

In Study 003, a total of 614 subjects were randomized into the study (306 subjects to the paroxetine mesylate group and 308 subjects to the placebo group). A similar percentage of subjects in both groups completed the study; 271 of the 306 randomized in the paroxetine group (88.6%) and 278 of the 308 subjects randomized to placebo (90.3%). Details of subject disposition in Study 003 are summarized in Table 3.

Table 3 Study 003: Disposition of Subjects

Disposition	Paroxetine mesylate n (%)	Placebo n (%)	Total n (%)
Number randomized	306	308	614
Received ≥ 1 dose of study drug*	301 (98.4)	305 (99.0)	606 (98.7)
Completed study	271 (88.6)	278 (90.3)	549 (89.4)
Discontinued from study	35 (11.4)	30 (9.7)	65 (10.6)
Reasons for Discontinuation			
• Adverse Event/Serious Adverse Event	8 (2.6)	4 (1.3)	12 (2.0)
• Subject request	8 (2.6)	12 (3.9)	20 (3.3)
• Columbia Suicide Severity Rating Scale – Baseline	5 (1.6)	2 (0.6)	7 (1.1)
• Investigator opinion that study would be detrimental to well-being	2 (0.7)	1 (0.3)	3 (0.5)
• Non-compliance to study requirements	1 (0.3)	2 (0.6)	3 (0.5)
• Other: not specified	0	1 (0.3)	1 (0.2)
• Other: eligibility criteria not met	2 (0.7)	4 (1.3)	6 (1.0)
• Other: lack of efficacy	2 (0.7)	0	2 (0.3)
• Other: lost to follow-up	5 (1.6)	4 (1.3)	9 (1.5)
• Other: non-compliance	1 (0.3)	0	1 (0.2)
• Other: withdrew consent	1 (0.3)	1 (0.3)	2 (0.3)

*** According to the Applicant's response on 01/07/2013, drug intake was unknown for 4 subjects in the paroxetine mesylate group and 3 subjects in the placebo group. They were counted as having received at least one dose of study medication by FDA.**
Source: Applicant's CSR for Study N30-003, Page 72, Table 7

In Study 004, a total of 570 subjects were randomized into the study (285 subjects to the paroxetine group and 285 subjects to the placebo group). All but one of the randomized subjects (99.8%) received at least one dose of study drug (placebo subject 53-008 did not receive any study drug). A total of 82.5% of the paroxetine group and 76.5% of the placebo group completed the study. Details of subject disposition in Study 004 are summarized in Table 4.

Table 4 Study 004: Disposition of Subjects

Disposition	Paroxetine mesylate n (%)	Placebo n (%)	Total n (%)
Number randomized	285	285	570
Received ≥ 1 dose of study drug	285 (100)	284 (99.6)	569 (99.8)
Completed study	235 (82.5)	218 (76.5)	453 (79.5)
Discontinued from study	50 (17.5)	67 (23.5)	117 (20.5)
Reasons for Discontinuation			
• Adverse Event/Serious Adverse Event	15 (5.3)	15 (5.3)	30 (5.3)
• Subject request	15 (5.3)	35 (12.3)	50 (8.8)
• Suicidality Tracking Scale	3 (1.1)	1 (0.4)	4 (0.7)
• Investigator opinion that study would be detrimental to well-being	0 (0.0)	2 (0.7)	2 (0.4)
• Non-compliance to study requirements	1 (0.4)	4 (1.4)	5 (0.9)
• Other: not specified	0 (0.0)	1 (0.4)	1 (0.2)
• Other: elective surgery	1 (0.4)	0 (0.0)	1 (0.2)
• Other: eligibility criteria not met	1 (0.4)	2 (0.7)	3 (0.5)
• Other: lack of efficacy	0 (0.0)	2 (0.7)	2 (0.4)
• Other: lost to follow-up	9 (3.2)	3 (1.1)	12 (2.1)
• Other: non-compliance	1 (0.4)	1 (0.4)	2 (0.4)
• Withdrew consent	2 (0.7)	0 (0.0)	2 (0.4)
• Relocation	2 (0.7)	1 (0.4)	3 (0.5)

Source: Applicant's CSR, Study N30-004, Page 69, Table 8

4.2 Demographic and Baseline Characteristics

Demographic and baseline characteristics for all treated subjects are presented in Table 5 and Table 6. Across both studies, more than 60% of subjects were white. The mean age of subjects was 54-55 years. At baseline, the mean BMI was 28-29 kg/m^2. More than 80% of subjects were naturally menopausal in each study.

Table 5 Study 003: Demographics and Baseline Characteristics (MITT Population)

Parameter		Paroxetine mesylate N=301	Placebo N=305	Total N=606
Age (years)	Mean	54.9	54.5	54.7
	Median	54.0	53.0	54.0
	Min-Max	40-73	40-79	40-79
Race, n (%)	Caucasian	190 (63.1)	202 (66.2)	392 (64.7)
	Black	106 (35.2)	93 (30.5)	199 (32.8)
	American Indian	2 (0.7)	1 (0.3)	3 (0.5)
	Asian	1 (0.3)	1 (0.3)	2 (0.3)
	Other	2 (0.7)	8 (2.6)	10 (1.7)
Ethnicity, n (%)	Hispanic/Latina	27 (9.0)	37 (12.1)	64 (10.6)
Height (in)	Mean	64.5	64.4	64.4
	Min-Max	56-72	57-73	56-73
Weight (lb)	Mean	173	175	174
	Min-Max	80-389	98-338	80-389
BMI (kg/m^2)	Mean	29.3	29.7	29.5
	Min-Max	16.8-60.7	19.0-56.5	16.8-60.7
Daily number of mod-severe hot flushes	Mean	11.8	11.7	11.7
	Median	10.4	10.4	10.4
Daily hot flush severity score	Mean	2.5	2.5	2.5
	Median	2.5	2.5	2.5
Menopause type, n (%)	Natural	242 (80.4)	253 (83.0)	495 (81.7)
	Surgical	59 (19.6)	52 (17.0)	111 (18.3)

Source: Adapted from Applicant's Summary of Clinical Efficacy (SCE), Page 43, Table 8

Table 6 Study 004: Demographics and Baseline Characteristics (MITT Population)

Parameter		Paroxetine mesylate N=284	Placebo N=284	Total N=568
Age (years)	Mean	54.2	54.5	54.4
	Median	54.0	54.0	54.0
	Min-Max	40-70	40-74	40-74
Race, n (%)	Caucasian	205 (72.2)	224 (78.9)	429 (75.5)
	Black	64 (24.3)	53 (18.7)	122 (21.5)
	Asian	3 (1.1)	6 (2.1)	9 (1.6)
	Other	7 (2.5)	1 (0.4)	8 (1.4)
Ethnicity, n (%)	Hispanic/Latina	16 (5.6)	21 (7.4)	37 (6.5)
Height (in)	Mean	64.9	64.3	64.6
	Min-Max	54-72	53-72	53-72
Weight (lb)	Mean	166.5	166.4	166.5
	Min-Max	107-263	100-274	100-274
BMI (kg/m^2)	Mean	28.0	28.3	28.1
	Min-Max	18.3-40.6	18.7-39.6	18.3-40.6
Daily number of mod-severe hot flushes	Mean	10.8	10.9	10.9
	Median	9.9	9.6	9.7
Daily hot flush severity score	Mean	2.5	2.5	2.5
	Median	2.5	2.5	2.5
Menopause type, n (%)	Natural	227 (79.9)	230 (81.0)	457 (80.5)
	Surgical	57 (20.1)	54 (19.0)	111 (19.5)

Source: Adapted from Applicant's SCE, Page 44, Table 9

4.3 Efficacy Findings

4.3.1 Statistical Issues in Efficacy Analysis

As per protocol, to support this indication, efficacy needed to be demonstrated with respect to all four co-primary endpoints. In addition, the Applicant agreed to conduct secondary supportive analyses on the clinical meaningfulness of the reduction in VMS frequency if the placebo-adjusted change from baseline in the daily hot flushes was < 2, and to demonstrate the persistence of efficacy at Week 24 in at least one study.

The Applicant had pre-specified an alternate analysis in case the data were not determined to be normally distributed. Due to the violation of the normality assumption for the data for each co-primary endpoint, the Applicant and FDA analyzed each endpoint by the pre-specified rank–ANCOVA method; i.e., an ANCOVA analysis on rank-transformed data.

In addition, FDA's analyses also included graphical presentation of the medians of change in the average daily frequency and severity over time and reported the difference between medians at Weeks 4 and 12, which provided a better estimate for the treatment effect of paroxetine mesylate relative to placebo for the skewed data.

4.3.2 Primary Efficacy Endpoint and Analysis

Results are summarized in Table 7 and depicted in Figure 1. Subjects had a median of about 10 daily moderate to severe hot flushes at baseline. Overall, the placebo-adjusted median

reduction of average daily frequency of hot flushes was consistent across the two studies at Week 4 (estimated median differences of 1.2 and 1.3 in Study 003 and Study 004, respectively). However, the improvement at Week 12 appeared to diminish by about one-fourth in Study 003 (estimated median difference: 0.9), while efficacy was maintained in Study 004 (estimated median difference: 1.7). The comparisons between paroxetine mesylate and placebo on the reduction of average daily frequency of hot flushes at both Weeks 4 and 12 achieved statistical significance in both studies (p-values <0.05).

Subjects had a median hot flush severity score of about 2.50. The placebo-adjusted median reduction of average daily severity of hot flushes was small in both studies at Weeks 4 and 12, ranging from 0.03 to 0.05. The comparisons between paroxetine mesylate and placebo on the reduction of the average daily severity of hot flushes achieved statistical significance at Week 4 in both studies, but at Week 12 in Study 004 only.

Sensitivity analyses of the co-primary endpoints were conducted for the MITT population to evaluate the robustness of the data and the impact of subject withdrawal. These analyses used LOCF imputation for missing data points, (e.g., from subjects who were withdrawn prematurely or discontinued from the treatment). The results of this analysis were consistent and similar to the primary analysis results using the observed data only.

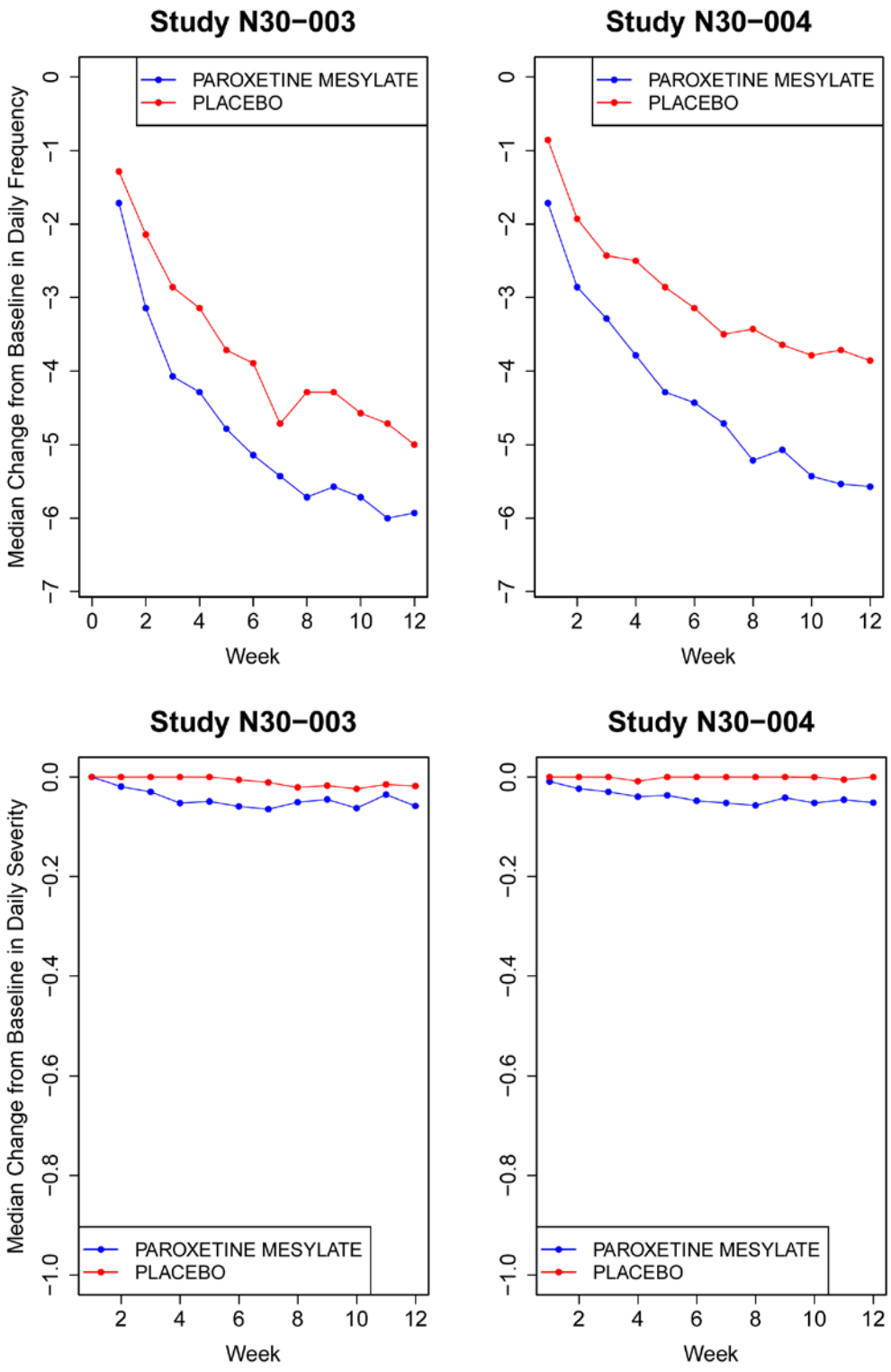
Table 7 Changes in Daily Frequency and Severity of Moderate to Severe Hot Flushes at Weeks 4 and 12 (MITT Population)

Study	Frequency			Severity		
	Paroxetine mesylate	Placebo	Treatment Difference	Paroxetine mesylate	Placebo	Treatment Difference
Study N30-003						
Baseline						
N	301	305		301	305	
Median	10.4	10.4		2.54	2.54	
Change from baseline						
Week 4						
Median	-4.3	-3.1	-1.2	-0.05	0.00	-0.05
p-value#			<0.0001			0.002
Week 12						
Median	-5.9	-5.0	-0.9	-0.06	-0.02	-0.04
p-value#			0.009			0.166
Study N30-004						
Baseline						
N	284	284		284	284	
Median	9.9	9.6		2.53	2.53	
Change from baseline						
Week 4						
Median	-3.8	-2.5	-1.3	-0.04	-0.01	-0.03
p-value#			<0.0001			0.037
Week 12						
Median	-5.6	-3.9	-1.7	-0.05	0.00	-0.05
p-value#			0.0001			0.006

*** Treatment Difference is the observed difference between medians.**
 # p-value is obtained from rank-ANCOVA model.
Sources: Applicant's Table 14.2.2.01A1 and Table 14.2.2.01_SEVA1 in n30-003-responsetables.pdf (dated 12/07/2012); Table 14.2.2.01A1 and Table 14.2.2.01_SEVA1 in n30-003-responsetables.pdf (dated 12/07/2012); FDA Reviewer's analysis

The median changes from baseline in daily frequency and severity of moderate to severe hot flushes over weeks by treatment groups are displayed in Figure 1.

Figure 1 Median Change from Baseline in Daily Frequency and Severity of Moderate to Severe Hot Flushes



4.3.3 Determination of Clinical Meaningfulness of Change in Frequency

As shown above, the estimated median difference on frequency reduction of moderate to severe hot flushes between paroxetine mesylate and placebo was < 2 hot flushes per day. Therefore, the analysis to evaluate whether this improvement is clinically meaningful according to the subject's overall assessment of the treatment benefit based on a "patient global improvement" anchoring question as described in Section 3.3.2 was conducted in Study 003 (Study 004 had already been initiated at the time the FDA and the Applicant discussed the specifics of the desired evaluation).

For this analysis, the subjects in the MITT population, irrespective of treatment assignment, were categorized as satisfied vs. non-satisfied based on the PGI questionnaire results at Weeks 4 and 12, respectively. The satisfied subjects were defined as those whose PGI response was ≤ 2, and unsatisfied subjects were defined as those whose PGI response was > 2. Next, a ROC analysis was conducted by fitting a logistic regression model with "satisfied vs. unsatisfied" as the response variable and change from baseline in daily frequency of moderate and severe hot flushes as the covariate at Weeks 4 and 12, respectively.

To maximize the sum of sensitivity and specificity, the cutoff values for change from baseline in daily frequency of moderate to severe hot flushes were -4.0 and -5.3 at Weeks 4 and 12, respectively. Subjects were classified as responders if the change from baseline was < -4.0 at Week 4; or < -5.3 at Week 12. Otherwise, subjects (including those with missing data) were classified as non-responders. At Week 4, 50% of subjects in the paroxetine group and 37% of subjects in the placebo group were responders (nominal p-value 0.001). At Week 12, 51% of subjects in the paroxetine group and 43% of subjects in the placebo group were responders (nominal p-value 0.055) (see Table 8).

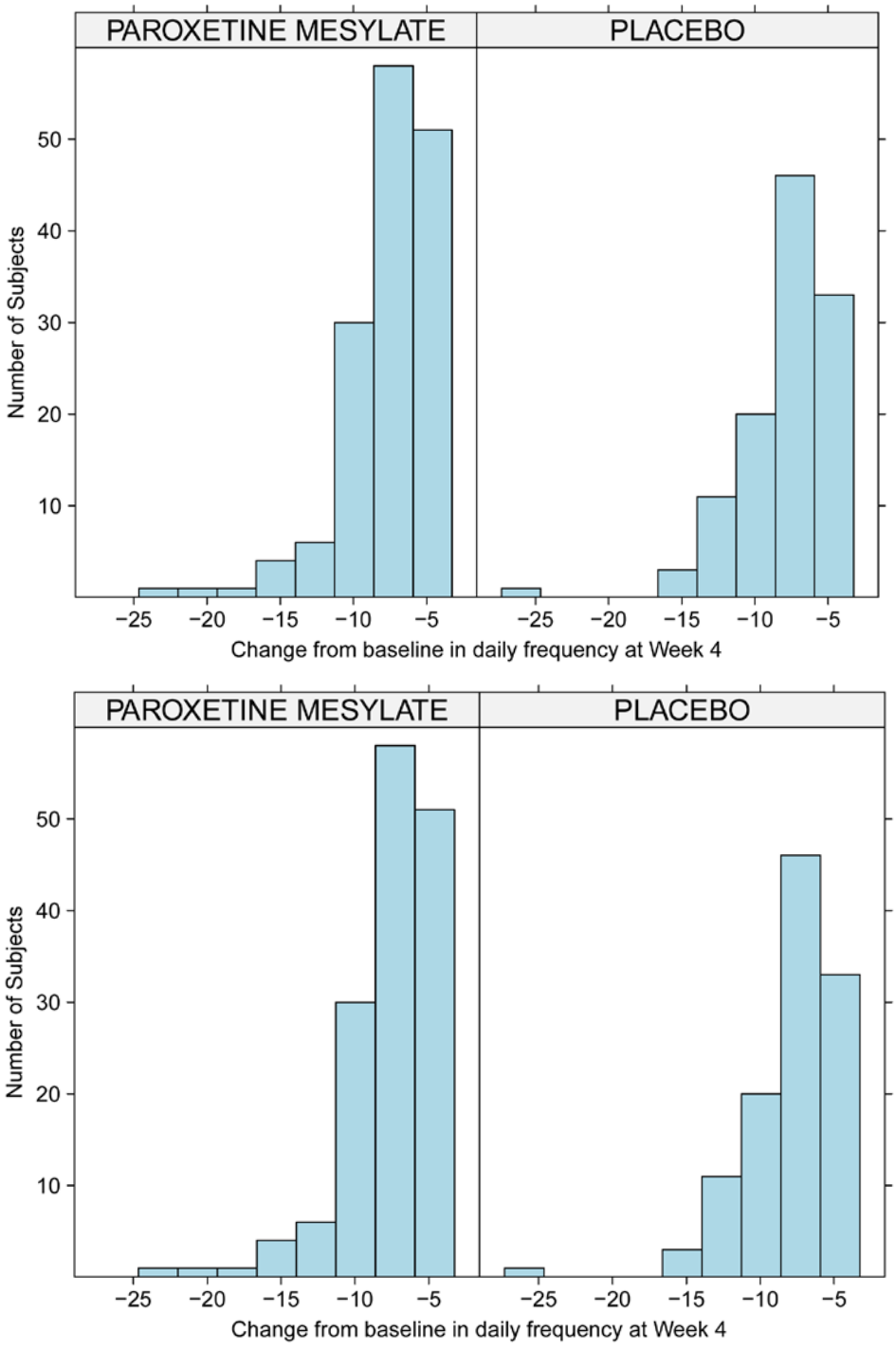
Table 8 Study 003: Percent of responders based on ROC cut-off (PGI ≤ 2 definition) MITT population

Visit	Cutoff	Statistics	Paroxetine mesylate n/N (%)	Placebo n/N (%)	Nominal p-value*
Week 4	-4.0	Responder	152/301 (50%)	114/305 (37%)	0.001
Week 12	-5.3	Responder	153/301 (51%)	131/305 (43%)	0.055

*p-value is obtained from a logit model adjusting for baseline average daily frequency.
Source: FDA analysis

Regardless of treatment assignment, the median change from baseline in daily frequency was -6.9 in the responders and -1.6 in the non-responders at Week 4. At Week 12, the mean change from baseline in daily frequency was -8.3 in the responders and -2.6 in the non-responders. Figure 2 presents the histograms of change from baseline in daily frequency of hot flushes in responders (as defined above) at Weeks 4 and 12 by treatment groups. As seen from the two histograms, the distributions of change from baseline in daily frequency of hot flushes were similar for the two treatment groups at both weeks.

Figure 2 Study 003: Change from Baseline in VMS Frequency among Responders, by Treatment Arm



FDA Comments

- **The majority of responders experienced VMS reductions of about 5-10 hot flushes/day.**
- **The median baseline frequency of VMS was higher in responders (11.4 hot flushes/day) than in non-responders (9.9 hot flushes/day). Within responders, the median baseline frequency was slightly higher among placebo subjects (11.6) than paroxetine subjects**

(11.0). Baseline frequency was not considered in the selection of cutoff values, but was accounted for in comparing the response rates between treatment arms.

- **The number of subjects experiencing large reductions in VMS frequency (e.g., -15 or greater) appears similar across treatment arms.**

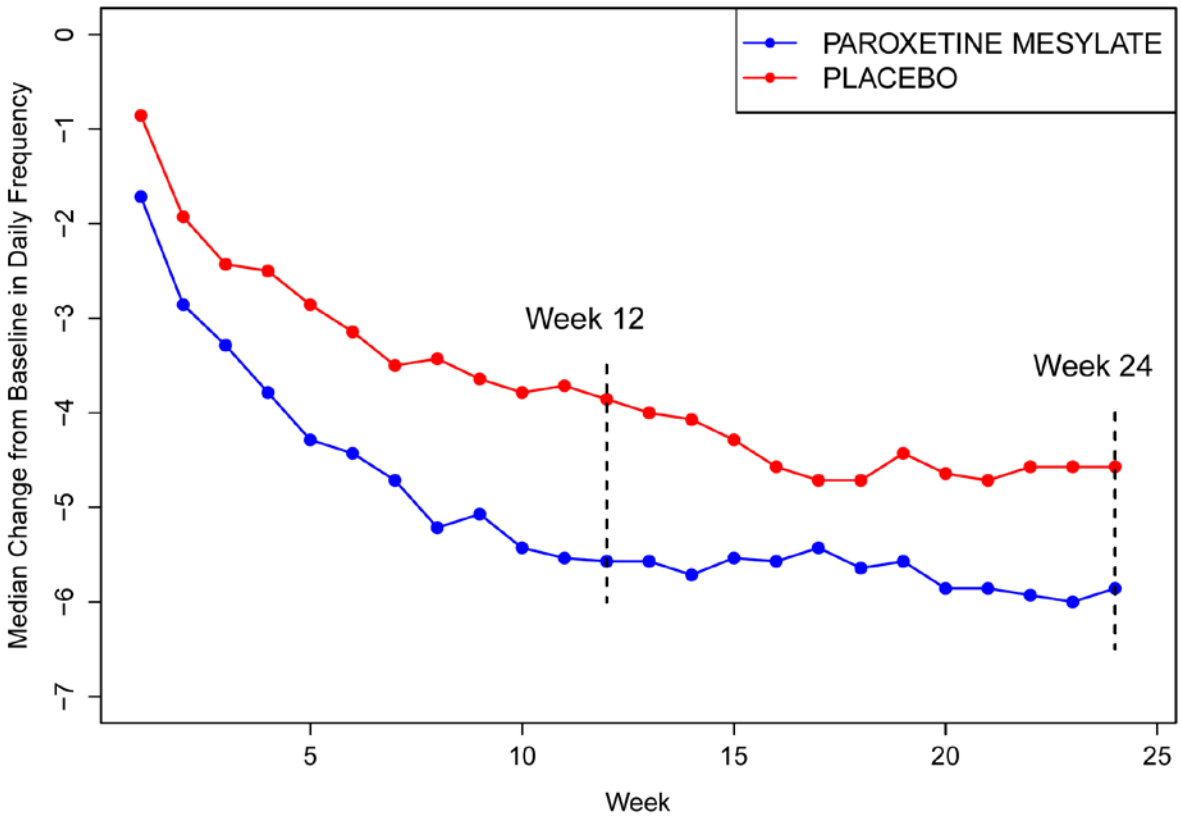
4.3.4 Treatment Benefit at Week 24

Treatment benefit for reduction of VMS frequency at Week 24 was explored descriptively in Study 004 by plotting the medians and median changes in average daily frequency of moderate to severe hot flushes over time and analyzed using a responder analysis. In this analysis, responders were defined as subjects who achieved ≥ 50% reduction from baseline in the frequency of moderate to severe hot flushes at Week 24. Non-responders were defined as those who had < 50% reduction at Week 24 or who prematurely discontinued the study.

Based on the MITT population, 47.5% of paroxetine mesylate-treated subjects achieved ≥ 50% reduction from baseline at Week 24 in the frequency of moderate to severe hot flushes compared to 36.3% of placebo-treated subjects (nominal p-value 0.0066, logit model).

Figure 3 shows the median change from baseline in VMS frequency over treatment weeks.

Figure 3 Study 004: Median Change from Baseline in Daily Frequency of Moderate to Severe VMS



Source: FDA analysis

4.3.5 Post Hoc Subgroup Analysis Results

Subgroups based on race/ethnicity and menopausal etiology were evaluated by the FDA statistical reviewer; these are routine exploratory analyses.

FDA Comment

The subgroup analyses showed no consistent and remarkable findings on the treatment effect in the subgroups across the two studies.

4.4 Overall Summary of Efficacy

The data from the two phase 3 studies showed that

1. Paroxetine mesylate 7.5 mg demonstrated statistically significant reductions from baseline in the daily frequency of moderate to severe hot flushes at Week 4 and Week 12 compared to placebo in both studies.
2. Paroxetine mesylate 7.5 mg demonstrated statistically significant reductions from baseline in the daily severity of moderate to severe hot flushes at Week 4 in both studies, but failed to meet criteria for statistical significance at Week 12 in Study 003.
3. In Study 003, a clinically meaningful improvement in VMS frequency was demonstrated at Week 4 based on the comparison of responder rates in the paroxetine mesylate and placebo groups, but not at Week 12.
4. In Study 004, a treatment effect on VMS frequency was demonstrated at Week 24.

5. Safety Finding from Paroxetine Mesylate Clinical Trials

5.1 Overview of the Safety Database for Paroxetine Mesylate

In addition to postmarketing safety information on the approved Pexeva product, evaluation of paroxetine mesylate safety is based on the database from this clinical development program that includes data from one phase 1, one phase 2 study, and two phase 3 studies that evaluated a single dose of paroxetine mesylate administered once daily in the evening as a 7.5 mg capsule. A total of 1,300 subjects were treated in the paroxetine mesylate clinical program, of which 659 subjects received at least one dose of paroxetine; with the remainder receiving at least one dose of placebo. Of these, 235 subjects in the paroxetine group and 218 in the placebo group completed 24 weeks of treatment in Study 004. The safety analysis set was defined as all subjects in phase 2 or 3 studies who took at least one dose of study drug and had at least one post-dose safety assessment. The number of subjects and duration of exposure for the safety database is shown in Table 9.

Table 9 Drug Exposure by Duration, Pooled Safety Dataset

Category	Paroxetine mesylate N=635 n (%)	Placebo N=641 n (%)
≥1 day to ≤4 weeks	27 (4.3)	28 (4.4)
>4 weeks to ≤12 weeks	224 (35.3)	249 (38.8)
>12 weeks to ≤24 weeks	357 (56.2)	343 (53.5)
>24 weeks	14 (2.2)	13 (2.0)

Source: Applicant's Summary of Clinical Safety (SCS), Page 34, Table 6

FDA Comments

- **At the Pre-NDA Meeting of May 29, 2012, the FDA stated that pooling the safety data from the two phase 3 trials and from the supporting phase 2 trial was acceptable.**
- **Safety data from the phase 1 pharmacokinetic study (Study N30-005) was not integrated into the data set. This study population enrolled basically healthy women and a placebo/comparator was not used in this study.**

5.2 Deaths

One death occurred in the paroxetine clinical program, in Study 003. This subject was a 55 year old African-American female who experienced a cardiorespiratory arrest 68 days after starting treatment with paroxetine mesylate. She died one day later, and was listed as having two serious adverse events (SAEs): coronary artery arteriosclerosis and cardiorespiratory arrest. She had a medical history of hypertension and had been taking Benazepril for about 15 years. Hypercholesterolemia was diagnosed about one year before the event. At the Screening Visit, her height was 64 inches and her weight was 184 lbs. Her blood pressure at Screening was 146/86 mm Hg with a pulse of 68 beats/min. Her screening electrocardiogram (ECG) was read as abnormal and not clinically significant. Both SAEs were not considered by the Investigator to be related to study drug.

FDA Comment
Given the limited information currently available, it is not possible to determine whether or not this was likely to be a drug-related death.

5.3 Non-fatal Serious Adverse Events

SAEs were reported in 14 subjects (2.2%) in the paroxetine group and nine subjects (1.4%) in the placebo group in the pooled safety database. With the exception of the single death in Study 003 study, the SAEs in the remaining 13 paroxetine subjects were all reported in the 24-week Study 004, while the SAEs in the nine subjects in the placebo group were reported across the phase 2 (1 subject) and phase 3 (8 subjects; 1 in Study 003 and 7 in Study 004) studies.

The most common SAEs reported in the paroxetine mesylate group were suicidal ideation (three subjects) and appendicitis (two subjects). All nonfatal SAEs in the paroxetine group resolved without sequelae. SAEs that occurred in either treatment arm are listed in Table 10.

Table 10 Serious Adverse Events, Pooled Safety Dataset

System Organ Class (SOC)	Subject #	Drug	Age Race	Action Taken (paroxetine arm only)	AE start (treatment day)
Gastrointestinal disorders					
Abdominal distension	N30-004-33-035*	Placebo	57 African American		157
Abdominal pain	N30-004-45-019	Paroxetine Mesylate	59 African American	Drug withdrawn	10
Colitis	N30-002-08-008*	Placebo	40 Caucasian		10
Dysphagia	N30-004-79-035*	Paroxetine Mesylate	52 African American	Drug continued	161
Gastrointestinal hemorrhage	N30-004-18-006	Placebo	53 Caucasian		110
Infections and Infestations					
Appendicitis	N30-004-03-029	Paroxetine Mesylate	46 African American	Drug interrupted	119
	N30-004-48-010	Paroxetine Mesylate	49 African American	Drug interrupted	73
Clostridium difficile colitis	N30-002-08-008*	Placebo	40 Caucasian		21
Sinusitis	N30-004-14-014	Paroxetine Mesylate	53 Caucasian	Drug interrupted	6
Musculoskeletal and connective tissue disorders					
Osteoarthritis	N30-004-70-002	Placebo	61 Caucasian		28
	N30-004-79-035*	Paroxetine Mesylate	52 African American	Drug continued	-6
Arthritis	N30-004-48-012	Paroxetine Mesylate	68 Caucasian	Drug continued	73
Psychiatric disorders					
Suicidal ideation	N30-004-05-013	Paroxetine Mesylate	60 Asian	Drug withdrawn	167
	N30-004-22-004	Paroxetine Mesylate	53 Caucasian	Drug continued	175
	N30-004-23-023	Paroxetine Mesylate	67 Caucasian	Drug continued	169
Suicide attempt	N30-004-23-014	Paroxetine Mesylate	50 Caucasian	Drug withdrawn	55
Hepatobiliary disorders					
Cholecystitis	N30-004-33-035*	Placebo	57 African American		155
	N30-004-75-007	Paroxetine Mesylate	51 African American	Drug continued	1
Biliary dyskinesia	N30-004-16-023	Paroxetine Mesylate	47 African American	Drug withdrawn	122

System Organ Class (SOC)	Subject #	Drug	Age Race	Action Taken (paroxetine arm only)	AE start (treatment day)
Injury, poisoning and procedural complications					
Acetabulum fracture Femur fracture	N30-004-02-001	Placebo	54 African American		120
Upper limb fracture	N30-003-47-028	Placebo	57 Caucasian		68
Cardiac disorders					
Arteriosclerosis coronary artery Cardio-respiratory arrest	N30-003-47-020	Paroxetine Mesylate	55 African American	Subject died	69
Neoplasms benign, malignant and unspecified (including cysts and polyps)					
Endometrial cancer	N30-004-79-005	Placebo	55 Caucasian		37
Squamous cell carcinoma of the chest	N30-004-33-051	Placebo	56 Caucasian		78
General disorders and administration site conditions					
Chest pain	N30-004-47-005	Placebo	67 Caucasian		152
Respiratory, thoracic and mediastinal disorders					
Asthma	N30-004-04-028	Paroxetine Mesylate	55 African American	Drug continued	114

***Subject also recorded for an SAE in a different SOC.**
Source: Medical Officer's analysis of SAEs using MAED program.

FDA Comment
The main SAEs of concern based on this listing are suicidal ideation/suicide attempt, which occurred exclusively in the paroxetine group, and are further discussed in Section 5.5.

5.4 Discontinuations due to Adverse Events

A total of 28 subjects (4.4%) in the paroxetine mesylate group and 21 subjects (3.3%) in the placebo group had adverse events (AEs) leading to study drug discontinuation. The most frequently reported AEs (abdominal pain, herpes zoster, disturbance in attention, headache, anxiety and suicidal ideation) resulting in discontinuation each occurred in only two subjects. AEs leading to discontinuation that occurred more frequently in the paroxetine group are listed in Table 11.

Table 11 Adverse Events Leading to Study Drug Discontinuation that Occurred More Frequently in the Paroxetine Group, Pooled Safety Dataset

MedDRA Preferred Term	Paroxetine mesylate N=635 n (%)	Placebo N=641 n (%)
Subjects with ≥ 1 AE	28 (4.4)	21 (3.3)
Abdominal pain	2 (0.3)	0 (0.0)
Herpes Zoster	2 (0.3)	0 (0.0)
Disturbance in attention	2 (0.3)	1 (0.2)
Headache	2 (0.3)	1 (0.2)
Suicidal ideation	2 (0.3)	0 (0.0)
Abdominal distension	1 (0.2)	0 (0.0)
Gingival bleeding	1 (0.2)	0 (0.0)
Chest discomfort	1 (0.2)	0 (0.0)
Depressed mood	1 (0.2)	0 (0.0)
Elevated mood	1 (0.2)	0 (0.0)
Suicide attempt	1 (0.2)	0 (0.0)

Source: Adapted from SCS, Page 57, Table 22

FDA Comment

AEs plausibly related to study drug that led to discontinuation clustered around CNS effects (disturbance in attention in two paroxetine subjects and one placebo subject) and mood effects (suicidal ideation, depressed mood, elevated mood and suicide attempt, collectively in five paroxetine subjects and no placebo subjects). However, anxiety led to discontinuation more often in placebo subjects than paroxetine subjects.

5.5 Other Adverse Events of Interest

The FDA clinical reviewer evaluated a variety of Standardized MedDRA Queries (SMQs) in the pooled safety dataset. This provides a useful screening tool to look at patterns of related AE terms across different System Organ Classes (SOCs). Otherwise, individual listings of AE terms may obscure detection of a possible clinical condition for which preferred terms are typically reported across different SOCs. However, SMQs cast a broad net and do not necessarily identify specific cases of the SMQ item, only potential cases.

Selected SMQs thought to be potentially relevant to paroxetine that occurred in > 1% of paroxetine subjects and at an incidence greater than those in placebo are displayed in Table 12.

Table 12 AE Frequency of Selected SMQs in > 1% of the Paroxetine Group and at an Incidence Greater than Placebo, Pooled Safety Dataset

	Paroxetine mesylate N = 641		Placebo N = 645	
SMQ (Broad Search)	**N**	**%**	**N**	**%**
Anticholinergic syndrome	42	6.6	36	5.6
Acute pancreatitis	40	6.2	28	4.3
Noninfectious encephalopathy/delirium	35	5.5	27	4.2
Noninfectious encephalitis	29	4.5	24	3.7
Depression and suicide/self-injury	26	4.1	12	1.9
Noninfectious meningitis	24	3.7	23	3.6
Anaphylactic reaction	21	3.3	21	3.3
Depression (excluding suicide and self injury)	21	3.3	12	1.9
Dementia	21	3.3	12	1.9
Hearing and vestibular disorders	19	3.0	8	1.2
Retroperitoneal fibrosis	18	2.8	17	2.6
Vestibular disorders	15	2.3	7	1.1

***SMQ = Standardized MedDRA Queries are groupings of terms from one or more SOCs that relate to a defined medical condition**
Source: Reviewer's analysis, adapted from MAEDS

The following events were pre-specified by the Applicant in the Statistical Analysis Plan as being of specific interest, based on AEs commonly reported for the drug classes of SSRIs and/or SNRIs. In addition, AEs suggestive of serotonin syndrome, hyponatremia, bone fracture, activation of mania/hypomania, seizures, akathisia, hallucinations, and sexual dysfunction (events noted as Precautions in current labeling) were evaluated. None were reported in ≥ 1% of paroxetine subjects and with at least twice the incidence of placebo.

Suicidality

Suicidality was prospectively assessed in all four clinical studies. In Studies 002 and 004, the Suicidality Tracking Scale (STS) was used, and was administered at baseline as well as on-treatment. The FDA subsequently recommended the use of the Columbia Suicide Severity Rating Scale (C-SSRS) in a Guidance (Suicidality: Prospective Assessment of Occurrence in Clinical Trials, September 2010) so in Studies 003 and 005, the C-SSRS was used, and was administered at baseline and on-treatment. For data pooling, STS scores were mapped using the domains defined in the Columbia Classification Algorithm for Suicide Assessment (C-CASA).

The Applicant used the following categories to assess suicidality in the phase 3 studies (the number of subjects in each treatment arm who fell into one or more of these categories is displayed in Table 13):

1. **Completed suicides**
2. **Suicide attempts**
3. **Spontaneous treatment-emergent suicidal ideation/behavior** reported as an AE/SAE leading to study discontinuation

4. **Suicidality events (suicidal behavior and/or ideation)** reported as an AE/SAE as a result of the of completion of the:
   - C-SSRS suicidal behavior/ideation:
   - STS suicidal behavior/ideation: Based on a total STS score > 0 at any time point during the study
5. **Early discontinuations** due to meeting the pre-specified STS or C-SSRS score discontinuation criteria

Table 13 Assessment of Suicidality

Criterion for Suicidality	Phase 1 Study 005 24 paroxetine	Phase 2 Study 002 49 paroxetine 52 placebo	Phase 3 Study 003 306 paroxetine 308 placebo	Phase 3 Study 004 285 paroxetine 285 placebo
Completed suicide	0	0	0	0
Suicide attempt	0	0	0	1 paroxetine 0 placebo
Treatment-emergent suicidal ideation, reported as AE/SAE	0	0	0	6 paroxetine 1 placebo
C-SSRS-reported suicidal behavior	0	NA	0	NA
C-SSRS-reported suicidal ideation	0	NA	0	NA
STS-reported suicidal behavior	NA	0 paroxetine 1 placebo	NA	6 paroxetine 4 placebo)
STS-reported suicidal ideation	NA	2 paroxetine 4 placebo	NA	27 paroxetine 29 placebo
Met C-SSRS criteria for discontinuation	0	NA	0*	NA
Met STS criteria for discontinuation	NA	0	0	3 paroxetine 1 placebo

*** Two subjects, one in each arm, met C-SSRS criteria for exclusion at baseline, but were inadvertently enrolled, then were discontinued shortly after starting study drug. They are not counted in this table, but are included in the safety population.**
NA = not applicable; instrument not used
Source: Clinical reviewer's tabulation

FDA Comment
The Applicant identified "suicidality" (used here to encompass suicide attempts/suicidal behavior and suicidal ideation) both on the basis of AEs/SAEs and on the basis of responses to the suicidality instruments. Some of these suicidality events were detected both as an AE/SAE and based on the subject's response and some were detected only when the subject provided a triggering response on the suicidality instrument. It is likely that relying only on AE/SAE reporting would result in under-detection of suicidality, but it is unclear to what extent relying on the screening instruments results in "false positive" reports of suicidality.

In phase 1 Study 005, there were no completed suicides or suicide attempts. There was also no spontaneous treatment-emergent suicidal behavior and/or ideation that led to premature discontinuation from the study and no reported C-SSRS-emergent events of suicidal behavior or ideation.

In phase 2 Study 002, which used the STS, discontinuation criteria based on STS score were not pre-specified. There were no completed or attempted suicides in this study. There were no events of STS-emergent suicidal behavior in the paroxetine group (0/49) and one event in the placebo group (1/52; 1.9%). There were a total of six events of STS-emergent suicidal ideation in six subjects, of whom two subjects (2/49; 4.1%) were in the paroxetine group and four subjects (4/52; 7.7%) were in the placebo group. There was no STS-emergent suicidal behavior and/or suicidal ideation that led to a premature discontinuation in this study.

There were no cases of suicide attempt, C-SSRS-emergent suicidal ideation or suicidal behavior in either treatment arm in Study 003.

In Study 004, based on an STS total score > 0 at any point during the study, there were a total of 56 events of STS-emergent suicidal ideation (which were not reported as AEs or SAEs), of which 27 events were in the paroxetine group and 29 were in the placebo group. There were four paroxetine subjects who reported SAEs of suicide attempt/suicidal ideation and three who reported AEs of suicidal ideation (one subject was counted in both categories, but is reported here as an SAE case). In the placebo arms, no subjects had SAEs of suicide attempt/suicidal ideation and one had an AE of suicidal ideation (see Table 14).

Subject medical/psychiatric history data was not summarized in the submission. Exclusion criteria for both phase 3 studies included a history of self-injurious behavior, suicidal ideation, depression, generalized anxiety, psychotic disorders, borderline personality disorders and Post Traumatic Stress Disorder.

Table 14 Cases of Suicide Attempt/Ideation and Suicidal Ideation, Pooled Phase 3 Dataset

Study #/ Subject ID	Suicide Ideation/Attempt	Age (years) Race	Day of Onset	Reported AE/SAE	Drug/ Outcome
Suicide Attempt Resulting in an SAE					
N30-004/ 4-23-014	Suicide attempt with multiple non-study drug overdose; she reported suicidal thoughts; had past history of overusing prescription drugs & past mental health hospitalization, but had 0 scores on STS at baseline and early termination	50 Caucasian	54	**-SAE** -Suicide attempt	**Paroxetine** Discontinued
STS-Emergent Suicidal Ideation Resulting in an SAE					
N30-004/ 4-05-013*	STS-emergent suicidal ideation: indicated taking active steps to prepare for suicide attempt and intentional injury. When contacted, stated she thought about suicide "a little" but did not have specific plan. (Also met pre-specified STS discontinuation criteria: at baseline indicated wish to be dead)	61 Asian	166	**-SAE** -Suicidal ideation	**Paroxetine** Discontinued - Recovered without sequelae
N30-004/ 4-22-004	STS-emergent suicidal ideation: indicated wish to be dead, think about suicide, plan for suicide and taking active steps to prepare for suicide attempt	53 Caucasian	174	**-SAE** -Suicidal ideation -	**Paroxetine** Not discontinued - Recovered without sequelae
N30-004/ 4-23-023	STS-emergent suicidal ideation: indicated wish to be dead, and think about suicide. Subject also had dx of metastatic cancer.	67 Caucasian	168	**-SAE** -Suicidal ideation	**Paroxetine** Not discontinued– Recovered without sequelae
STS-Emergent Suicidal Ideation Resulting in an AE					
N30-004/ 4-48-022	STS-emergent suicidal ideation: indicated wish to be dead and think about suicide	50 African-American	83	**-AE** -Suicidal ideation	**Paroxetine** Discontinued
N30-004/ 4-45-017	Met pre-specified STS criteria for discontinuation: indicated wish to be dead, want to harm self and think about suicide	70 Caucasian	Took 2 doses	**-AE** -Suicidal ideation	**Paroxetine** Discontinued
N30-004/ 4-50-004	Met pre-specified STS criteria for discontinuation: indicated wish to be dead and want to harm self	66 Caucasian	83	**-AE** -Suicidal ideation	**Paroxetine** Discontinued
N30-004/ 4-73-026	Met pre-specified STS criteria for discontinuation: indicated wish to be dead and think about suicide	49 Caucasian	87	**-**No -Suicidal ideation	**Placebo** Discontinued

***Subject 4-05-013 was discontinued from the study due to an AE/SAE of suicidal ideation and also due to pre-specified discontinuation criteria based on STS score; therefore, the subject was counted as an AE and an SAE**
Source: SCS, Adapted from section on suicidality, page 63

FDA Comments

- **It is notable that all cases of suicidality reported in the phase 3 trials occurred in Study 004. Study 004 was of longer duration, but four of the seven events in paroxetine subjects occurred in the first 12 weeks of the trial, so it is not clear that duration of exposure is a relevant factor.**
- **It is clear that the incidence of suicidality, while low, is greater in women treated with paroxetine mesylate. Such an effect is described in class labeling for all antidepressant drugs. The Division of Psychiatry Products has been consulted to advise us whether actions beyond class labeling are warranted to address this effect.**

Cardiovascular Events

Cardiovascular AEs are reported in Table 15.

Table 15 Cardiovascular AEs, Pooled Safety Dataset

MedDRA Preferred Term	Paroxetine N=635 n (%)	Placebo N=641 n (%)
Subjects with ≥ 1 TEAE	27 (4.3)	17 (2.7)
Hypertension*	7 (1.1)	3 (0.5)
Chest pain	4 (0.6)	1 (0.2)
Peripheral edema	4 (0.6)	1 (0.2)
Palpitations	3 (0.5)	2 (0.3)
EKG abnormal	3 (0.5)	1 (0.2)
Increased blood pressure*	1 (0.2)	7 (1.1)
Arrhythmia	1 (0.2)	0 (0.0)
Arteriosclerosis coronary artery	1 (0.2)	0 (0.0)
Cardio-respiratory arrest	1 (0.2)	0 (0.0)
Ventricular dysfunction	1 (0.2)	0 (0.0)
Chest discomfort	1 (0.2)	0 (0.0)
Cardiac murmur	1 (0.2)	0 (0.0)
Prolonged QT interval	1 (0.2)	0 (0.0)
Heart rate increased	1 (0.2)	0 (0.0)
Heart rate irregular	1 (0.2)	0 (0.0)

*** "Hypertension" was reported as an AE based on a diagnosis, while "blood pressure increased" was reported based on the subject's blood pressure measurement**
Source: Applicant's SCS, Page 60, Table 23

FDA Comments

- **Although the incidence of reported hypertension was numerically higher with paroxetine, objective blood pressure data were similar in the two treatment groups (see Section 5.5).**
- **Other than the one reported death in a paroxetine subject in Study 003, there were no cardiovascular events reported as SAEs.**
- **Chest discomfort (Subject 4-22-014 in the paroxetine group) was the only cardiovascular event resulting in discontinuation of study drug.**

Hepatic Events

The rate of hepatic AEs (reported as abnormal liver function test, increased transaminases, increased ALT and increased hepatic enzymes) was higher in the pooled placebo arms (0.9%) than the pooled paroxetine arms (0.5%) over the pooled safety dataset. There were no hepatic SAEs or AEs that led to discontinuation.

FDA Comment

The Applicant stated that hepatic events were pre-specified mainly due to safety signals observed with the SNRI desvenlafaxine. In concert with the lack of laboratory signals relating to liver enzymes, paroxetine does not appear to have an adverse impact on the liver in this database.

Gastrointestinal or Other Bleeding Events

SSRIs are associated with an increased risk of gastrointestinal (GI) bleeds as well as bleeding at other sites, likely due to reduced platelet serotonin. Table 16 displays the incidence of GI and other bleeding events that occurred more frequently in paroxetine subjects. In addition,

one placebo subject had an SAE of GI hemorrhage; two paroxetine and three placebo subjects discontinued due to one of these events.

Table 16 GI or Other Bleeding Events Occurring with Higher Incidence in Paroxetine Arm, Pooled Safety Dataset

MedDRA Preferred Term	Paroxetine N=635 n (%)	Placebo N=641 n (%)
Subjects with ≥ 1 TEAE	12 (1.9)	10 (1.6)
Vaginal hemorrhage or postmenopausal hemorrhage	6 (0.9)	6 (0.9)
Vitreous hemorrhage	1 (0.2)	0 (0.0)
Gingival bleeding	1 (0.2)	0 (0.0)
Rectal hemorrhage	1 (0.2)	0 (0.0)
Periorbital hematoma	1 (0.2)	0 (0.0)
Breast hematoma	1 (0.2)	0 (0.0)
Epistaxis	1 (0.2)	0 (0.0)

Source: Applicant's SCS, Page 63, Table 25

FDA Comment
The categories of "vaginal hemorrhage" and "postmenopausal hemorrhage" warrant further investigation, as vaginal/uterine bleeding is abnormal in postmenopausal women not using hormones.

5.6 Common Adverse Events

The most common AEs for the phase 3 studies are reported in Table 17, based on AEs that occurred in at least 2% of subjects and were more common among subjects in the paroxetine arms. Overall, 50% of subjects in the paroxetine group and 47% of subjects in the placebo group reported at least one adverse event. Results were similar when the entire pooled safety dataset was evaluated.

Table 17 Selected Common Adverse Events in the Phase 3 Studies (ITT Population)

System Organ Class Preferred Term	Paroxetine (n = 586) Frequency n (%)	Placebo (n = 589) Frequency n (%)
Infections and infestations		
Nasopharyngitis	30 (5.1%)	29 (4.9%)
Bronchitis	11 (1.9%)	3 (0.5%)
Urinary tract infection	10 (1.7%)	8 (1.4%)
Influenza	9 (1.5%)	8 (1.4%)
Nervous system disorders		
Headache	25 (4.3%)	22 (3.7%)
Dizziness	12 (2.0%)	5 (0.8%)
Gastrointestinal disorders		
Nausea	22 (3.8%)	8 (1.4%)
Diarrhea	17 (2.9%)	15 (2.5%)
Dry mouth	9 (1.5%)	7 (1.2%)
Musculoskeletal and connective tissue disorders		
Back pain	10 (1.7%)	9 (1.5%)
General disorders and administration site conditions		
Fatigue	20 (3.4%)	9 (1.5%)
Psychiatric disorders		
Abnormal dreams	6 (1.0%)	4 (0.7%)
Mood swings	6 (1.0%)	3 (0.5%)
Respiratory, thoracic and mediastinal disorders		
Cough	7 (1.2%)	2 (0.3%)
Oropharyngeal pain	6 (1.0%)	3 (0.5%)
Skin and subcutaneous tissue disorders		
Rash	6 (1.0%)	3 (0.5%)
Reproductive system and breast disorders		
Vaginal hemorrhage	6 (1.0%)	3 (0.5%)
Vascular disorders		
Hypertension	6 (1.0%)	3 (0.5%)

Source: Applicant's SCS, Page 47, Table 16

FDA Comments

- **AEs that occurred at a notably higher incidence in paroxetine subjects and are plausibly drug-related include dizziness, nausea, fatigue and mood swings.**
- **Overall, there do not appear to be major differences in the incidence of common AEs between treatment arms.**

5.7 Adverse Events after Discontinuation of Paroxetine Mesylate

In the clinical trials, subjects were started on paroxetine mesylate without titration, and were discontinued from the drug without tapering. A Discontinuation-Emergent Signs and Symptoms (DESS) checklist was administered seven days after the last dose of study drug. "Old symptoms" were defined as symptoms that appeared before the seven days prior to the administration of the DESS, were present while taking study drug, and continued into the seven-day period. "New symptoms" were those that appeared after discontinuation of study

drug and within the seven days prior to administration of the DESS. The results from the phase 3 trials are shown in

Table 18 Summary of DESS, Pooled Safety Dataset

DESS Category	Paroxetine N=635 n (%)	Placebo N=641 n (%)
Old Symptoms present	405 (100)	414 (100)
Old symptoms worsened	102 (25.2%)	73 (17.6%)
New symptom: None	394 (62.0)	429 (66.9)
One or more	112 (17.6)	88 (13.7)
Most commonly occurring new symptoms		
Increased dreaming or nightmares	4.9%	3.1%
Muscle cramps, spasms or twitching	3.5%	1.4%
Headache	3.1%	2.3%
Muscle aches or pains	2.7%	2.2%
Nervousness or anxiety	2.7%	1.9%
Fatigue, tiredness	2.5%	1.4%
Restless feeling in the legs	2.5%	1.1%
Trouble sleeping, insomnia	2.4%	1.1%

Source: SCS, Table 42, p 99

FDA Comments

- **About 15% of subjects developed new symptoms during the week after discontinuation, and the incidence of new symptoms did not differ much between paroxetine and placebo subjects. Certain symptoms, such as muscle cramps/spasms/ twitching, restless feeling in the legs, and trouble sleeping/insomnia were reported in the paroxetine group at twice the incidence of the placebo group; these may warrant inclusion in labeling.**
- **Overall, there does not appear to be a need for titration or tapering when initiating or discontinuing dosing, respectively.**

5.8 Vital Signs

There were no clinically relevant differences in vital signs between the paroxetine and placebo groups in the pooled safety database.

5.9 Laboratory Findings

Assessment of mean hematological values over time showed no clinically relevant differences between the paroxetine and placebo groups. In general, the mean values for the various parameters remained within their normal ranges from baseline to the end of the study.

Clinical chemistries included albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, bilirubin, blood urea nitrogen, calcium, chloride, creatinine kinase, creatinine, plasma glucose, lactate dehydrogenase, magnesium, phosphorus, potassium, sodium, total protein, and uric acid. Shift tables for chemistry parameters for the paroxetine group showed no clinically meaningful changes over time.

5.10 Electrocardiograms

All three studies evaluated routinely conducted ECGs as "normal," "abnormal, not clinically significant (ABN, NCS)," and "abnormal, clinically significant (ABN, CS)" based on the investigator's assessment. Shifts in readings from baseline to on-treatment are shown in Table 19.

Table 19 Shift Table of ECG Results, Pooled Safety Dataset

	Paroxetine mesylate N=635 n (%)			Placebo N=641 n (%)		
Baseline Category	**ABN, CS**	**ABN, NCS**	**Normal**	**ABN, CS**	**ABN, NCS**	**Normal**
ABN, CS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
ABN, NCS	1 (0.2)	154 (24.3)	84 (13.2)	1 (0.2)	155 (24.2)	82 (12.8)
Normal	2 (0.3)	66 (10.4)	297 (46.8)	1 (0.2)	71 (11.1)	301 (47.0)

Source: Applicant's ISS, Page 125, Table 75

No clinically relevant changes were observed between the groups. Three subjects (0.5%) in the paroxetine group and two (0.3%) subjects in the placebo group shifted from a normal or not clinically significant reading at baseline to a clinically significant abnormal ECG at the end of the study. No trends were apparent based on these findings.

5.11 Concomitant Use of Paroxetine Mesylate with Tamoxifen

Issues currently under review include the question of concomitant use of paroxetine mesylate in women who are taking tamoxifen. The current Pexeva label states

> *Some studies have shown that the efficacy of tamoxifen, as measured by the risk of breast cancer relapse/mortality, may be reduced when co-prescribed with paroxetine as a result of paroxetine's irreversible inhibition of CYP2D6…However, other studies have failed to demonstrate such a risk. It is uncertain whether the co-administration of paroxetine and tamoxifen has a significant adverse effect on the efficacy of tamoxifen. When tamoxifen is used for the treatment or prevention of breast cancer, prescribers should consider using an alternative antidepressant with little or not CYP2D6 inhibition.*

However, use of tamoxifen is not listed as a contraindication to use of Pexeva.

In contrast, the Nolvadex (tamoxifen) label, states only that

> *Tamoxifen is extensively metabolized after oral administration. N-desmethyl tamoxifen is the major metabolite found in patients' plasma. The biological activity of N-desmethyl tamoxifen appears to be similar to that of tamoxifen. 4-Hydroxytamoxifen and a side chain primary alcohol derivative of tamoxifen have been identified as minor metabolites in plasma. Tamoxifen is a substrate of cytochrome P-450 3A, 2C9 and 2D6, and an inhibitor of P-glycoprotein.*

The Nolvadex label does not discuss a drug-drug interaction with paroxetine and does not contraindicate or discuss concomitant administration with paroxetine.

A 2006 FDA advisory committee recommended that tamoxifen labeling be revised to indicate that patients who take CYP2D6 inhibitors such as paroxetine have significant

reductions in plasma concentration of the active metabolite that is formed after CYP2D6-mediated metabolism of N-desmethyl tamoxifen.

FDA Comment
This is an important consideration because women with breast cancer or at high risk of breast cancer, who may be taking tamoxifen, constitute a significant target population for nonhormonal VMS therapies. DRUP will be discussing this issue further with the Division of Oncology Products 1.

5.12 Postmarketing Safety Reports

Based on postmarketing safety data on Pexeva that was submitted during the review cycle, no significant change in the safety profile of Pexeva was observed. A literature search did not identify any new AEs reported with paroxetine treatment. No clinical studies have been initiated or completed with paroxetine mesylate 7.5 mg since the NDA submission.

FDA Comment
This review did not reveal any new or unlabeled safety issues relating to paroxetine mesylate.

5.13 Summary of Safety

A summary of AEs reported across the pooled safety dataset is shown in Table 20.

Table 20 Summary of AEs, Pooled Safety Dataset

Category	Paroxetine mesylate N=635[2] n (%)	Placebo N=641[3] n (%)
Subjects with any TEAE[1]	320 (50.4)	301 (47.0)
Deaths	1 (0.2)	0 (0)
Subjects with SAEs	14 (2.2)	9 (1.4)
Subjects with study drug discontinuations due to a TEAE	28 (4.4)	21 (3.3)
Subjects with suicidality	7 (1.1)	1 (0.2)
Subjects with a cardiovascular TEAE	27 (4.3)	17 (2.7)
Subjects with a hepatic TEAE	3 (0.5)	6 (0.9)
Subjects with gastrointestinal or bleeding TEAE	12 (1.9)	10 (1.6)

[1] TEAE: Any AE that started or worsened on or after the day of first dose
[2] A subject is counted only once within each category
Source: SCS, Page 43, Table 12

Overall, the incidence of SAEs, TEAEs generally and AEs of specific interest did not differ much by treatment arm. CNS and mood-related AEs occurred more frequently among subjects on paroxetine, as did suicidality-related events, albeit at a low rate. Currently labeling addresses the risk of suicidality and of interference with cognitive and motor performance.

Appendices

1. **Approved Labeling for Pexeva**

2. **Draft Guidance for Industry, Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation, January 2003**

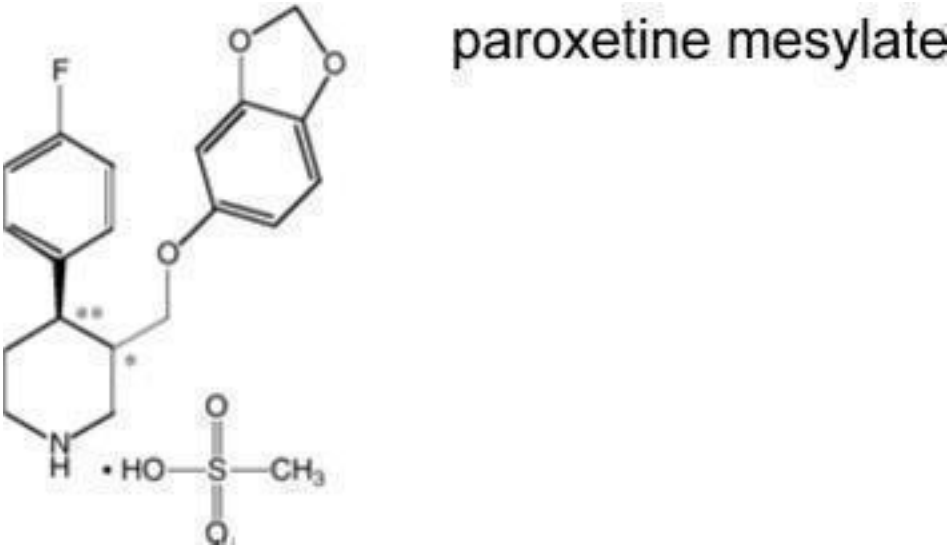
3. **Schedule of Events, Phase 3 Studies**

PEXEVA - paroxetine mesylate tablet, film coated
NOVEN THERAPEUTICS, LLC

Suicidality and Antidepressant Drugs
Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of PEXEVA® (paroxetine mesylate) or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. PEXEVA® (paroxetine mesylate) is not approved for use in pediatric patients. (See Warnings: Clinical Worsening and Suicide Risk, Precautions: Information for Patients, and Precautions: Pediatric Use.)

DESCRIPTION

PEXEVA® (paroxetine mesylate) is an orally administered psychotropic drug with a chemical structure related to paroxetine hydrochloride (Paxil®). It is the mesylate salt of a phenylpiperidine compound identified chemically as (-)-*trans*-4R-(4'-fluorophenyl)-3S-[(3',4'-methylenedioxyphenoxy) methyl] piperidine mesylate and has the empirical formula of $C_{19}H_{20}FNO_3 \cdot CH_3SO_3H$. The molecular weight is 425.5 (329.4 as free base). The structural formula is:



Paroxetine mesylate is an odorless, off-white powder, having a melting point range of 147° to 150°C and a solubility of more than 1 g/ml in water.

Tablets

Each oval, film-coated tablet contains paroxetine mesylate equivalent to paroxetine as follows: 10 mg (white); 20 mg (scored, dark orange); 30 mg (yellow); 40 mg (rose). Inactive ingredients consist of dibasic calcium phosphate, hydroxypropyl methylcellulose, hydroxypropylcellulose, magnesium stearate, sodium starch glycolate, titanium dioxide, ferric oxide red (C.I. 77491) (20 mg and 40 mg only) and ferric oxide yellow (C.I. 77492) (20 mg, 30 mg, and 40 mg only).

CLINICAL PHARMACOLOGY

Pharmacodynamics

The efficacy of paroxetine in the treatment of MDD, OCD, panic disorder (PD), and generalized anxiety disorder (GAD) is presumed to be linked to potentiation of serotonergic activity in the central nervous system resulting from inhibition of neuronal reuptake of serotonin (5-hydroxy-tryptamine, 5-HT). Studies at clinically relevant doses in humans have demonstrated that paroxetine blocks the uptake of serotonin into human platelets. *In vitro* studies in animals also suggest that paroxetine is a potent and highly selective inhibitor of neuronal serotonin reuptake and has only very weak effects on norepinephrine and dopamine neuronal reuptake. *In vitro* radioligand binding studies indicate that paroxetine has little affinity for muscarinic alpha1-, alpha2-, beta-adrenergic-, dopamine

(D2)-, 5-HT1-, 5-HT2-, and histamine (H1)-receptors; antagonism of muscarinic, histaminergic, and alpha1-adrenergic receptors has been associated with various anticholinergic, sedative, and cardiovascular effects for other psychotropic drugs.
Because the relative potencies of paroxetine's major metabolites are at most 1/50 of the parent compound, they are essentially inactive.

Pharmacokinetics
Paroxetine mesylate is completely absorbed after oral dosing of the mesylate salt. In a study in which normal male subjects (n=25) received paroxetine 30 mg tablets daily for 24 days, steady-state paroxetine concentrations were achieved by approximately 13 days for most subjects, although it may take substantially longer in an occasional patient. At steady state, mean values of C_{max}, T_{max}, C_{min}, and $T_{1/2}$ were 81.3 ng/ml (CV 41%), 8.1 hr. (CV 56%), 43.2 ng/ml (CV 52%), and 33.2 hr. (CV 52%), respectively. The steady-state C_{max} and C_{min} values were about 7 and 10 times what would be predicted from single dose studies. Steady-state drug exposure based on AUC_{0-24} was about 10 times greater than would have been predicted from single-dose data in these subjects. The excess accumulation is a consequence of the fact that one of the enzymes that metabolizes paroxetine is readily saturable.
In steady-state dose proportionality studies involving elderly and nonelderly patients, at doses of 20 to 40 mg daily for the elderly and 20 to 50 mg daily for the nonelderly, some nonlinearity was observed in both populations, again reflecting a saturable metabolic pathway. In comparison to C_{min} values after 20 mg daily, values after 40 mg were only about 2 to 3 times greater than doubled.
The effects of food on the bioavailability of paroxetine were studied in subjects administered a single dose with and without food. AUC was only slightly increased (6%) when drug was administered with food but the C_{max} was 29% greater, while the time to reach peak plasma concentration decreased from 6.4 hours post-dosing to 4.9 hours.
Paroxetine is extensively metabolized after oral administration. The principal metabolites are polar and conjugated products of oxidation and methylation, which are readily cleared. Conjugates with glucuronic acid and sulfate predominate, and major metabolites have been isolated and identified. Data indicate that the metabolites have no more than 1/50 the potency of the parent compound at inhibiting serotonin uptake. The metabolism of paroxetine is accomplished in part by cytochrome CYP2D6. Saturation of this enzyme at clinical doses appears to account for the nonlinearity of paroxetine kinetics with increasing dose and increasing duration of treatment. The role of this enzyme in paroxetine metabolism also suggests potential drug-drug interactions (see PRECAUTIONS).
Approximately 64% of a 30 mg oral solution dose of paroxetine was excreted in the urine with 2% as the parent compound and 62% as metabolites over a 10-day post-dosing period. About 36% was excreted in the feces (probably via the bile), mostly as metabolites and less than 1% as the parent compound over the 10-day post-dosing period.
In a meta analysis of paroxetine from 4 studies done in healthy volunteers following multiple dosing of 20 mg/day to 40 mg/day, males did not exhibit a significantly lower C_{max} or AUC than females.
Distribution: Paroxetine distributes throughout the body, including the CNS, with only 1% remaining in the plasma.

Protein Binding: Approximately 95% and 93% of paroxetine is bound to plasma protein at 100 ng/ml and 400 ng/ml, respectively. Under clinical conditions, paroxetine concentrations would normally be less than 400 ng/ml. Paroxetine does not alter the *in vitro* protein binding of phenytoin or warfarin.

Renal and Liver Disease: Increased plasma concentrations of paroxetine occur in subjects with renal and hepatic impairment. The mean plasma concentrations in patients with creatinine clearance below 30 ml/min was approximately 4 times greater than seen in normal volunteers. Patients with creatinine clearance of 30 to 60 ml/min and patients with hepatic functional impairment had about a 2-fold increase in plasma concentrations (AUC, C_{max}).

The initial dosage should therefore be reduced in patients with severe renal or hepatic impairment, and upward titration, if necessary, should be at increased intervals (see DOSAGE AND ADMINISTRATION).

Elderly Patients: In a multiple-dose study in the elderly at daily paroxetine doses of 20, 30, and 40 mg, C_{min} concentrations were about 70% to 80% greater than the respective C_{min} concentrations in nonelderly subjects. Therefore the initial dosage in the elderly should be reduced (see DOSAGE AND ADMINISTRATION).

Drug-Drug Interactions: *In vitro* drug interaction studies reveal that paroxetine inhibits CYP2D6. Clinical drug interaction studies have been performed with substrates of CYP2D6 and show that paroxetine can inhibit the metabolism of drugs metabolized by CYP2D6 including desipramine, risperidone, and atomoxetine (see PRECAUTIONS—Drug Interactions).

Clinical Trials

Major Depressive Disorder
The efficacy of paroxetine as a treatment for MDD has been established in 6 placebo-controlled studies of patients with MDD (ages 18 to 73). In these studies paroxetine was shown to be significantly more effective than placebo in treating MDD by at least 2 of the following measures: Hamilton Depression Rating Scale (HDRS), the Hamilton depressed mood item, and the Clinical Global Impression (CGI)-Severity of Illness. Paroxetine was significantly better than placebo in improvement of the HDRS sub-factor scores, including the depressed mood item, sleep disturbance factor, and anxiety factor.

A study of outpatients with MDD who had responded to paroxetine (HDRS total score <8) during an initial 8-week open treatment phase and were then randomized to continuation on paroxetine or placebo for 1 year demonstrated a significantly lower relapse rate for patients taking paroxetine (15%) compared to those on placebo (39%). Effectiveness was similar for male and female patients.

Obsessive Compulsive Disorder

The effectiveness of paroxetine in the treatment OCD was demonstrated in two 12-week multicenter placebo-controlled studies of adult outpatients (Studies 1 and 2). Patients in all studies had moderate to severe OCD (DSM-IIIR) with mean baseline ratings on the Yale Brown Obsessive Compulsive Scale (YBOCS) total score ranging from 23 to 26. Study 1, a dose-range finding study where patients were treated with fixed doses of 20, 40, or 60 mg of paroxetine/day demonstrated that daily doses of paroxetine 40 and 60 mg are effective in the treatment of OCD. Patients receiving doses of 40 and 60 mg paroxetine experienced a mean reduction of approximately 6 and 7 points, respectively, on the YBOCS total score which was significantly greater than the approximate 4-point reduction at 20 mg and a 3-point reduction in the placebo-treated patients. Study 2 was a flexible dose study comparing paroxetine (20 to 60 mg daily) with clomipramine (25 to 250 mg daily). In this study, patients receiving paroxetine experienced a mean reduction of approximately 7 points on the YBOCS total score, which was significantly greater than the mean reduction of approximately 4 points in the placebo-treated patients.

The following table provides the outcome classification by treatment group on Global Improvement items of the Clinical Global Impressions (CGI) scale for Study 1.

Outcome Classification (%) on CGI-Global Improvement Item for Completers in Study 1

Outcome Classification	**Placebo (N=74)**	**Paroxetine 20 mg (N=75)**	**Paroxetine 40 mg (N=66)**	**Paroxetine 60 mg (N=66)**
Worse	14%	7%	7%	3%
No Change	44%	35%	22%	19%
Minimally Improved	24%	33%	29%	34%
Much Improved	11%	18%	22%	24%
Very Much Improved	7%	7%	20%	20%

Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of age or gender.

The long-term maintenance effects of paroxetine in OCD were demonstrated in a long-term extension to Study 1. Patients who were responders on paroxetine during the 3-month double-blind phase and a 6-month extension on open-label paroxetine (20 to 60 mg/day) were randomized to either paroxetine or placebo in a 6-month double-blind relapse prevention phase. Patients randomized to paroxetine were significantly less likely to relapse than comparably treated patients who were randomized to placebo.

Panic Disorder

The effectiveness of paroxetine in the treatment of PD was demonstrated in three 10- to 12-week multicenter, placebo-controlled studies of adult outpatients (Studies 1-3). Patients in all studies had PD (DSM-IIIR), with or without agoraphobia. In these studies, paroxetine was shown to be significantly more effective than placebo in treating PD by at least 2 out of 3 measures of panic attack frequency and on the Clinical Global Impression Severity of Illness score.

Study 1 was a 10-week dose-range finding study: patients were treated with fixed paroxetine doses of 10, 20, or 40 mg/day or placebo. A significant difference from placebo was observed only for the 40 mg/day group. At endpoint, 76% of patients receiving paroxetine 40 mg/day were free of panic attacks, compared to 44% of placebo-treated patients.

Study 2 was a 12-week flexible-dose study comparing paroxetine (10 to 60 mg daily) and placebo. At endpoint, 51% of paroxetine patients were free of panic attacks compared to 32% of placebo-treated patients.

Study 3 was a 12-week flexible-dose study comparing paroxetine (10 to 60 mg daily) to placebo in patients concurrently receiving standardized cognitive behavioral therapy. At endpoint, 33% of the paroxetine-treated patients showed a reduction to 0 or 1 panic attacks compared to 14% of placebo patients.

In both Studies 2 and 3, the mean paroxetine dose for completers at endpoint was approximately 40 mg/day of paroxetine.

Long-term maintenance effects of paroxetine in PD were demonstrated in an extension to Study 1. Patients who were responders during the 10-week double-blind phase and during a 3-month double-blind extension phase were randomized to either paroxetine (10, 20, or 40 mg/day) or placebo in a 3-month double-blind relapse prevention phase. Patients randomized to paroxetine were significantly less likely to relapse than comparably treated patients who were randomized to placebo.

Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of age or gender.

Generalized Anxiety Disorder
The effectiveness of paroxetine in the treatment of Generalized Anxiety Disorder (GAD) was demonstrated in two 8-week, multicenter, placebo-controlled studies (Studies 1 and 2) of adult outpatients with GAD (DSM-IV).

Study 1 was an 8-week study comparing fixed paroxetine doses of 20 mg or 40 mg/day with placebo. Doses of 20 mg or 40 mg of paroxetine were both demonstrated to be significantly superior to placebo on the Hamilton Rating Scale for Anxiety (HAM-A) total score. There was not sufficient evidence in this study to suggest a greater benefit for the 40 mg/day dose compared to the 20 mg/day dose.

Study 2 was a flexible-dose study comparing paroxetine (20 mg to 50 mg daily) and placebo. Paroxetine demonstrated statistically significant superiority over placebo on the Hamilton Rating Scale for Anxiety (HAM-A) total score. A third study, also flexible-dose comparing paroxetine (20 mg to 50 mg daily), did not demonstrate statistically significant superiority of paroxetine over placebo on the Hamilton Rating Scale for Anxiety (HAM-A) total score, the primary outcome.

Subgroup analyses did not indicate differences in treatment outcomes as a function of race or gender. There were insufficient elderly patients to conduct subgroup analyses on the basis of age.

In a longer-term trial, 566 patients meeting DSM-IV criteria for GAD, who had responded during a single-blind, 8-week acute treatment phase with 20 to 50 mg/day of paroxetine, were randomized to continuation of paroxetine at their same dose, or to placebo, for up to 24 weeks of observation for relapse. Response during the single-blind phase was defined by having a decrease of ≥2 points compared to baseline on the CGI-Severity of Illness scale, to a score of ≤3. Relapse during the double-blind phase was defined as an increase of ≥2 points compared to baseline on the CGI-Severity of Illness scale to a score of ≥4, or withdrawal due to lack of efficacy. Patients receiving continued paroxetine experienced a significantly lower relapse rate over the subsequent 24 weeks compared to those receiving placebo.

INDICATIONS AND USAGE

Major Depressive Disorder
PEXEVA® (paroxetine mesylate) is indicated for the treatment of MDD.
The efficacy of paroxetine in the treatment of a major depressive episode was established in 6-week controlled trials of outpatients whose diagnoses corresponded most closely to the DSM-III category of MDD (see CLINICAL PHARMACOLOGY). A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks); it should include at least 4 of the following 8 symptoms: change in appetite, change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and a suicide attempt or suicidal ideation.
The effects of paroxetine in hospitalized depressed patients have not been adequately studied.
The efficacy of paroxetine in maintaining a response in MDD for up to 1 year was demonstrated in a placebo-controlled trial (see CLINICAL PHARMACOLOGY). Nevertheless, the physician who elects to use PEXEVA® (paroxetine mesylate) for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

Obsessive Compulsive Disorder
PEXEVA® (paroxetine mesylate) is indicated for the treatment of obsessions and compulsions in patients with OCD as defined in the DSM-IV. The obsessions or compulsions cause marked distress, are time-consuming, or significantly interfere with social or occupational functioning.
The efficacy of paroxetine was established in two 12-week trials with obsessive compulsive outpatients whose diagnoses corresponded most closely to the DSM-IIIR category of OCD (see CLINICAL PHARMACOLOGY—Clinical Trials).
OCD is characterized by recurrent and persistent ideas, thoughts, impulses, or images (obsessions) that are egodystonic and/or repetitive, purposeful, and intentional behaviors (compulsions) that are recognized by the person as excessive or unreasonable.
Long-term maintenance of efficacy was demonstrated in a 6-month relapse prevention trial. In this trial, patients assigned to paroxetine showed a lower relapse rate compared to patients on placebo (see CLINICAL PHARMACOLOGY—Clinical Trials).
Nevertheless, the physician who elects to use PEXEVA® (paroxetine mesylate) for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Panic Disorder
PEXEVA® (paroxetine mesylate) is indicated for the treatment of PD, with or without agoraphobia, as defined in DSM-IV. PD is characterized by the occurrence of unexpected panic attacks and associated concern about having additional attacks, worry about the implications or consequences of the attacks, and/or a significant change in behavior related to the attacks.
The efficacy of paroxetine was established in three 10- to 12-week trials in PD patients whose diagnoses corresponded to the DSM-IIIR category of PD (see CLINICAL PHARMACOLOGY—Clinical Trials).

PD (DSM-IV) is characterized by recurrent unexpected panic attacks, ie, a discrete period of intense fear or discomfort in which 4 (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes: (1) palpitations, pounding heart, or accelerated heart rate; (2) sweating; (3) trembling or shaking; (4) sensations of shortness of breath or smothering; (5) feeling of choking; (6) chest pain or discomfort; (7) nausea or abdominal distress; (8) feeling dizzy, unsteady, lightheaded, or faint; (9) derealization (feelings of unreality) or depersonalization (being detached from oneself); (10) fear of losing control; (11) fear of dying; (12) paresthesias (numbness or tingling sensations); (13) chills or hot flushes.
Long-term maintenance of efficacy was demonstrated in a 3-month relapse prevention trial. In this trial, patients with PD assigned to paroxetine demonstrated a lower relapse rate compared to patients on placebo (see CLINICAL PHARMACOLOGY—Clinical Trials). Nevertheless, the physician who prescribes PEXEVA® (paroxetine mesylate) for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

Generalized Anxiety Disorder
Paroxetine is indicated for the treatment of Generalized Anxiety Disorder (GAD), as defined in DSM-IV. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.
The efficacy of paroxetine in the treatment of GAD was established in two 8-week placebo-controlled trials in adults with GAD. Paroxetine has not been studied in children or adolescents with Generalized Anxiety Disorder (see CLINICAL PHARMACOLOGY—Clinical Trials).
Generalized Anxiety Disorder (DSM-IV) is characterized by excessive anxiety and worry (apprehensive expectation) that is persistent for at least 6 months and which the person finds difficult to control. It must be associated with at least 3 of the following 6 symptoms: restlessness or feeling keyed up or on edge, being easily fatigued, difficulty concentrating or mind going blank, irritability, muscle tension, sleep disturbance.
The efficacy of paroxetine in maintaining a response in patients with Generalized Anxiety Disorder, who responded during an 8-week acute treatment phase while taking paroxetine and were then observed for relapse during a period of up to 24 weeks, was demonstrated in a placebo-controlled trial (see CLINICAL PHARMACOLOGY—Clinical Trials). Nevertheless, the physician who elects to use paroxetine for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS
The use of MAOIs intended to treat psychiatric disorders with PEXEVA® or within 14 days of stopping treatment with PEXEVA® is contraindicated because of an increased risk of serotonin syndrome. The use of PEXEVA® within 14 days of stopping an MAOI intended to treat psychiatric disorders is also contraindicated (see WARNINGS and DOSAGE AND ADMINISTRATION).
Starting PEXEVA® in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue is also contraindicated because of an increased risk of serotonin syndrome (see WARNINGS and DOSAGE AND ADMINISTRATION).
Concomitant use in patients taking thioridazine is contraindicated (see WARNINGS and PRECAUTIONS).
Concomitant use in patients taking pimozide is contraindicated (see PRECAUTIONS).
PEXEVA® (paroxetine mesylate) tablets are contraindicated in patients with a hypersensitivity to paroxetine or any of the inactive ingredients in PEXEVA® (paroxetine mesylate) tablets.

WARNINGS

Clinical Worsening and Suicide Risk
Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behaviour (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.
The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1.

TABLE 1

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, ie, beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see PRECAUTIONS and DOSAGE AND ADMINISTRATION —Discontinuation of Treatment with PEXEVA® (paroxetine mesylate), for a description of the risks of discontinuation of PEXEVA® (paroxetine mesylate)).

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for PEXEVA® (paroxetine mesylate) should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Screening Patients for Bipolar Disorder: A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that PEXEVA® (paroxetine mesylate) is not approved for use in treating bipolar depression.

Serotonin Syndrome: The development of a potentially life-threatening serotonin syndrome has been reported with SNRIs and SSRIs, including PEXEVA®, alone but particularly with concomitant use of other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort) and with drugs that impair metabolism of serotonin (in particular, MAOIs, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome.

The concomitant use of PEXEVA® with MAOIs intended to treat psychiatric disorders is contraindicated. PEXEVA® should also not be started in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue. All reports with methylene blue that provided information on the route of administration involved intravenous administration in the dose range of 1 mg/kg to 8 mg/kg. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection) or

at lower doses. There may be circumstances when it is necessary to initiate treatment with a MAOI such as linezolid or intravenous methylene blue in a patient taking PEXEVA®. PEXEVA® should be discontinued before initiating treatment with the MAOI (see CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION).
If concomitant use of PEXEVA® with other serotonergic drugs including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, buspirone, tryptophan, and St. John's Wort is clinically warranted, be aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases.
Treatment with PEXEVA® and any concomitant serotonergic agents should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

Potential Interaction with Thioridazine
Thioridazine administration alone produces prolongation of the QTc interval, which is associated with serious ventricular arrhythmias, such as torsade de pointes-type arrhythmias, and sudden death. This effect appears to be dose-related.
An *in vivo* study suggests that drugs which inhibit CYP2D6, such as paroxetine, will elevate plasma levels of thioridazine. Therefore, it is recommended that paroxetine not be used in combination with thioridazine (see CONTRAINDICATIONS and PRECAUTIONS).

Usage in Pregnancy
Teratogenic Effects: Epidemiological studies have shown that infants exposed to paroxetine in the first trimester of pregnancy have an increased risk of congenital malformations, particularly cardiovascular malformations. The findings from these studies are summarized below:

- A study based on Swedish national registry data demonstrated that infants exposed to paroxetine during pregnancy (n = 815) had an increased risk of cardiovascular malformations (2% risk in paroxetine-exposed infants) compared to the entire registry population (1% risk), for an odds ratio (OR) of 1.8 (95% confidence interval 1.1 to 2.8). No increase in the risk of overall congenital malformations was seen in the paroxetine-exposed infants. The cardiac malformations in the paroxetine-exposed infants were primarily ventricular septal defects (VSDs) and atrial septal defects (ASDs). Septal defects range in severity from those that resolve spontaneously to those which require surgery.

- A separate retrospective cohort study from the United States (United Healthcare data) evaluated 5,956 infants of mothers dispensed antidepressants during the first trimester (n = 815 for paroxetine). This study showed a trend towards an increased risk for cardiovascular malformations for paroxetine (risk of 1.5%) compared to other antidepressants (risk of 1%), for an OR of 1.5 (95% confidence interval 0.8 to 2.9). Of the 12 paroxetine-exposed infants with cardiovascular malformations, 9 had VSDs. This study also suggested an increased risk of overall major congenital malformations including cardiovascular defects for paroxetine (4% risk) compared to other (2% risk) antidepressants (OR 1.8; 95% confidence interval 1.2 to 2.8).

- Two large case-control studies using separate databases, each with >9,000 birth defect cases and >4,000 controls, found that maternal use of paroxetine during the first trimester of pregnancy was associated with a 2- to 3-fold increased risk of right ventricular outflow tract obstructions. In one study the OR was 2.5 (95% confidence interval, 1.0 to 6.0, 7 exposed infants) and in the other study the OR was 3.3 (95% confidence interval, 1.3 to 8.8, 6 exposed infants).

- Other studies have found varying results as to whether there was an increased risk of overall, cardiovascular, or specific congenital malformations. A meta-analysis of epidemiological data over a 16-year period (1992 to 2008) included a total of 20 distinct studies: 11 studies (including the above noted studies) reported estimates for both cardiovascular defects and overall congenital malformations, 3 studies reported estimates only for cardiovascular defects, and 6 studies reported estimates only for overall congenital malformations. While subject to limitations, this meta-analysis suggested an increased occurrence of cardiovascular malformations (prevalence odds ratio [POR] 1.5; 95% confidence interval 1.2 to 1.9) and overall malformations (POR 1.2; 95% confidence interval 1.1 to 1.4) with paroxetine use during the first trimester. It was not possible in this meta-analysis to determine the extent to which cardiovascular malformations might have contributed to overall malformations, nor was it possible to determine whether any specific types of cardiovascular malformations contributed to all cardiovascular malformations.

- If a patient becomes pregnant while taking paroxetine, she should be advised of the potential harm to the fetus. Unless the benefits of paroxetine to the mother justify continuing treatment, consideration should be given to either discontinuing paroxetine therapy or switching to another antidepressant (see PRECAUTIONS—Discontinuation of Treatment With PEXEVA®). For women who intend to become pregnant or are in their first trimester of pregnancy, paroxetine should only be initiated after consideration of the other available treatment options.

Animal Findings: Reproduction studies were performed at doses up to 50 mg/kg/day in rats and 6 mg/kg/day in rabbits administered during organogenesis. These doses are approximately 8 (rat) and 2 (rabbit) times the MRHD on an mg/m2 basis. These studies have revealed no evidence of teratogenic effects. However, in rats, there was an increase in pup deaths during the first 4 days of lactation when dosing occurred during the last trimester of gestation and continued throughout lactation. This effect occurred at a dose of 1 mg/

kg/day or approximately one-sixth of the MRHD on an mg/m2 basis. The no-effect dose for rat pup mortality was not determined. The cause of these deaths is not known.

Nonteratogenic Effects: Neonates exposed to PEXEVA® and other SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see WARNINGS: Serotonin Syndrome).

Infants exposed to SSRIs in pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1 – 2 per 1,000 live births in the general population and is associated with substantial neonatal morbidity and mortality. Several recent epidemiologic studies suggest a positive statistical association between SSRI use (including PEXEVA®) in pregnancy and PPHN. Other studies do not show a significant statistical association.

Physicians should also note the results of a prospective longitudinal study of 201 pregnant women with a history of major depression, who were either on antidepressants or had received antidepressants less than 12 weeks prior to their last menstrual period, and were in remission. Women who discontinued antidepressant medication during pregnancy showed a significant increase in relapse of their major depression compared to those women who remained on antidepressant medication throughout pregnancy.

When treating a pregnant woman with PEXEVA®, the physician should carefully consider both the potential risks of taking an SSRI, along with the established benefits of treating depression with an antidepressant. This decision can only be made on a case by case basis (see DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS, Postmarketing Reports).

PRECAUTIONS

General

Activation of Mania/Hypomania: During premarketing testing, hypomania or mania occurred in approximately 1.0% of paroxetine-treated unipolar patients compared to 1.1% of active-control and 0.3% of placebo-treated unipolar patients. In a subset of patients classified as bipolar, the rate of manic episodes was 2.2% for paroxetine and 11.6% for the combined active-control groups. As with all drugs effective in the treatment of MDD, paroxetine should be used cautiously in patients with a history of mania.

Seizures: During premarketing testing, seizures occurred in 0.1% of paroxetine-treated patients, a rate similar to that associated with other drugs effective in the treatment of MDD. Paroxetine should be used cautiously in patients with a history of seizures. It should be discontinued in any patient who develops seizures.

Discontinuation of Treatment with PEXEVA® (paroxetine mesylate): Recent clinical trials supporting the various approved indications for paroxetine employed a taper-phase regimen, rather than an abrupt discontinuation of treatment. The taper-phase regimen used in GAD and PTSD clinical trials involved an incremental decrease in the daily dose by 10 mg/day at weekly intervals. When a daily dose of 20 mg/day was reached, patients were continued on this dose for 1 week before treatment was stopped.

With this regimen in those studies, the following adverse events were reported at an incidence of 2% or greater for paroxetine at an incidence at least twice that reported for placebo: abnormal dreams, paresthesia, and dizziness. In the majority of patients, these events were mild to moderate and were self-limiting and did not require medical intervention.

During marketing of paroxetine and other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon the discontinuation of these drugs (particularly when abrupt), including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (eg, paresthesias such as electric shock sensations and tinnitus), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms.

Patients should be monitored for these symptoms when discontinuing treatment with paroxetine. A gradual reduction in the dose, rather than abrupt cessation, is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate (see DOSAGE and ADMINISTRATION).

See also PRECAUTIONS—Pediatric Use for adverse events reported upon discontinuation of treatment with paroxetine in pediatric patients.

Tamoxifen: Some studies have shown that the efficacy of tamoxifen, as measured by the risk of breast cancer relapse/mortality, may be reduced when co-prescribed with paroxetine as a result of paroxetine's irreversible inhibition of CYP2D6 (see Drug Interactions).

However, other studies have failed to demonstrate such a risk. It is uncertain whether the co-administration of paroxetine and tamoxifen has a significant adverse effect on the efficacy of tamoxifen. When tamoxifen is used for the treatment or prevention of breast cancer, prescribers should consider using an alternative antidepressant with little or no CYP2D6 inhibition.

Akathisia: The use of paroxetine or other SSRIs has been associated with the development of akathisia, which is characterized by an inner sense of restlessness and psychomotor agitation such as an inability to sit or stand still usually associated with subjective distress. This is most likely to occur within the first few weeks of treatment.

Hyponatremia: Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including PEXEVA® (paroxetine mesylate). In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than 110 mmol/L have been reported. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted may be at greater risk (see Geriatric Use). Discontinuation of PEXEVA® (paroxetine mesylate) should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted.

Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death.

Abnormal Bleeding: SSRIs and SNRIs, including PEXEVA® (paroxetine mesylate), may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anti-coagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages.

Patients should be cautioned about the risk of bleeding associated with the concomitant use of PEXEVA® (paroxetine mesylate) and NSAIDs, aspirin, or other drugs that affect coagulation.

Bone Fracture: Epidemiological studies on bone fracture risk following exposure to some antidepressants, including SSRIs, have reported an association between antidepressant treatment and fractures. There are multiple possible causes for this observation and it is unknown to what extent fracture risk is directly attributable to SSRI treatment. The possibility of a pathological fracture, that is, a fracture produced by minimal trauma in a patient with decreased bone mineral density, should be considered in patients treated with paroxetine who present with unexplained bone pain, point tenderness, swelling, or bruising.

Use in Patients with Concomitant Illness: Clinical experience with paroxetine in patients with certain concomitant systemic illness is limited. Caution is advisable in using paroxetine in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

As with other SSRIs, mydriasis has been infrequently reported in the premarketing studies with paroxetine. A few cases of acute angle closure glaucoma associated with paroxetine therapy have been reported in the literature. As mydriasis can cause acute angle closure in patients with narrow angle glaucoma, caution should be used when paroxetine is prescribed for patients with narrow angle glaucoma.

Paroxetine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product's premarket testing. Evaluation of electrocardiograms of 682 patients who received paroxetine in double-blind, placebo-controlled trials, however, did not indicate that paroxetine is associated with the development of significant ECG abnormalities. Similarly, paroxetine does not cause any clinically important changes in heart rate or blood pressure.

Increased plasma concentrations of paroxetine occur in patients with severe renal impairment (creatinine clearance <30 ml/min) or severe hepatic impairment. A lower starting dose should be used in such patients (see DOSAGE AND ADMINISTRATION).

Information for Patients

PEXEVA® (paroxetine mesylate) should not be chewed or crushed, and should be swallowed whole.

Patients should be cautioned about the risk of serotonin syndrome with the concomitant use of paroxetine and triptans, tramadol, or other serotonergic agents.

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with PEXEVA® (paroxetine mesylate) and should counsel them in its appropriate use. A patient Medication Guide about “Antidepressant Medicines, Depression and other Serious Mental Illness, and Suicidal Thoughts or Actions” is available for PEXEVA® (paroxetine mesylate). The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss

the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.
Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking PEXEVA® (paroxetine mesylate).
Clinical Worsening and Suicide Risk: Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

Drugs that Interfere with Hemostasis (NSAIDs, Aspirin, Warfarin, etc.): Patients should be cautioned about concomitant use of paroxetine with NSAIDs, aspirin, or other drugs that affect coagulation since the combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding.

Interference with Cognitive and Motor Performance: Any psychoactive drug may impair judgment, thinking, or motor skills. Although in controlled studies paroxetine has not been shown to impair psychomotor performance, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that paroxetine therapy does not affect their ability to engage in such activities.

Completing Course of Therapy: While patients may notice improvement with paroxetine therapy in 1 to 4 weeks, they should be advised to continue therapy as directed.

Concomitant Medication: Patients should be advised to inform their physician if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Alcohol: Although paroxetine has not been shown to increase the impairment of mental and motor skills caused by alcohol, patients should be advised to avoid alcohol while taking PEXEVA® (paroxetine mesylate).

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy (see WARNINGS—Usage in Pregnancy: Teratogenic and Nonteratogenic Effects).

Nursing: Patients should be advised to notify their physician if they are breast-feeding an infant (see PRECAUTIONS—Nursing Mothers).

Laboratory Tests
There are no specific laboratory tests recommended.

Paxil® (paroxetine hydrochloride)
Paroxetine, the active ingredient in PEXEVA® (paroxetine mesylate), is also the active ingredient of Paxil®. Thus, these two agents should not be coadministered.

Drug Interactions
Tryptophan: As with other serotonin reuptake inhibitors, an interaction between paroxetine and tryptophan may occur when they are coadministered. Adverse experiences, consisting primarily of headache, nausea, sweating, and dizziness, have been reported when tryptophan was administered to patients taking paroxetine. Consequently, concomitant use of paroxetine with tryptophan is not recommended.

Monoamine Oxidase Inhibitors: See CONTRAINDICATIONS and WARNINGS.

Pimozide: In a controlled study of healthy volunteers, after paroxetine was titrated to 60 mg daily, coadministration of a single dose of 2 mg pimozide was associated with mean increases in pimozide AUC of 151% and C_{max} of 62%, compared to pimozide administered alone. The increase in pimozide AUC and C_{max} is due to the CYP2D6 inhibitory properties of paroxetine. Due to the narrow therapeutic index of pimozide and its known ability to prolong the QT interval, concomitant use of pimozide and paroxetine is contraindicated (see CONTRAINDICATIONS).

Serotonergic Drugs: Based on the mechanism of action of paroxetine and the potential for serotonin syndrome, caution is advised when paroxetine is coadministered with other drugs or agents that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, fentanyl, tramadol, or St. John's Wort (see

WARNINGS—Serotonin Syndrome). The concomitant use of paroxetine with other SSRIs, SNRIs, or tryptophan is not recommended (see *PRECAUTIONS—Drug Interactions, Tryptophan*).

Thioridazine: See CONTRAINDICATIONS and WARNINGS.

Warfarin: Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis in the face of unaltered prothrombin time) between paroxetine and warfarin. Since there is little clinical experience, the concomitant administration of paroxetine and warfarin should be undertaken with caution (see PRECAUTIONS: Drugs That Interfere With Hemostasis).

Triptans: There have been rare postmarketing reports of serotonin syndrome with the use of an SSRI and a triptan. If concomitant use of paroxetine with a triptan is warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see WARNINGS—Serotonin Syndrome).

Drugs Affecting Hepatic Metabolism: The metabolism and pharmacokinetics of paroxetine may be affected by the induction or inhibition of drug-metabolizing enzymes.

Cimetidine— Cimetidine inhibits many cytochrome P450 (oxidative) enzymes. In a study where paroxetine (30 mg qd) was dosed orally for 4 weeks, steady-state plasma concentrations of paroxetine were increased by approximately 50% during coadministration with oral cimetidine (300 mg tid) for the final week. Therefore, when these drugs are administered concurrently, dosage adjustment of paroxetine after the 20 mg starting dose should be guided by clinical effect. The effect of paroxetine on cimetidine's pharmacokinetics was not studied.

Phenobarbital— Phenobarbital induces many cytochrome P450 (oxidative) enzymes. When a single oral 30 mg dose of paroxetine was administered at phenobarbital steady state (100 mg qd for 14 days), paroxetine AUC and $T_{1/2}$ were reduced (by an average of 25% and 38%, respectively) compared to paroxetine administered alone. The effect of paroxetine on phenobarbital pharmacokinetics was not studied. Since paroxetine exhibits nonlinear pharmacokinetics, the results of this study may not address the case where the 2 drugs are both being chronically dosed. No initial paroxetine dosage adjustment is considered necessary when coadministered with phenobarbital; any subsequent adjustment should be guided by clinical effect.

Phenytoin— When a single oral 30 mg dose of paroxetine was administered at phenytoin steady state (300 mg qd for 14 days), paroxetine AUC and $T_{1/2}$ were reduced (by an average of 50% and 35%, respectively) compared to paroxetine administered alone. In a separate study, when a single oral 300 mg dose of phenytoin was administered at paroxetine steady state (30 mg qd for 14 days), phenytoin AUC was slightly reduced (12% on average) compared to phenytoin administered alone. Since both drugs exhibit nonlinear pharmacokinetics, the above studies may not address the case where the 2 drugs are both being chronically dosed. No initial dosage adjustments are considered necessary when these drugs are coadministered; any subsequent adjustments should be guided by clinical effect (see ADVERSE REACTIONS—Postmarketing Reports).

Drugs Metabolized by Cytochrome CYP2D6: Many drugs, including most drugs effective in the treatment of MDD (paroxetine, other SSRIs, and many tricyclics), are metabolized by the cytochrome P450 isozyme CYP2D6. Like other agents that are metabolized by CYP2D6, paroxetine may significantly inhibit the activity of this isozyme. In most patients (>90%), this CYP2D6 isozyme is saturated early during paroxetine dosing. In one study, daily dosing of paroxetine (20 mg qd) under steady-state conditions increased single dose desipramine (100 mg) C_{max}, AUC, and $T_{1/2}$ by an average of approximately 2-, 5-, and 3-fold, respectively. Concomitant use of paroxetine with risperidone, a CYP2D6 substrate, has also been evaluated. In one study, daily dosing of paroxetine 20 mg in patients stabilized on risperidone (4 to 8 mg/day) increased mean plasma concentrations of risperidone approximately 4-fold, decreased 9-hydroxyrisperidone concentrations approximately 10%, and increased concentrations of the active moiety (the sum of risperidone plus 9-hydroxyrisperidone) approximately 1.4-fold. The effect of paroxetine on the pharmacokinetics of atomoxetine has been evaluated when both drugs were at steady state. In healthy volunteers who were extensive metabolizers of CYP2D6, paroxetine 20 mg daily was given in combination with 20 mg atomoxetine every 12 hours. This resulted in increases in steady state atomoxetine AUC values that were 6- to 8-fold greater and in atomoxetine C_{max} values that were 3- to 4-fold greater than when atomoxetine was given alone. Dosage adjustment of atomoxetine may be necessary and it is recommended that atomoxetine be initiated at a reduced dose when it is given with paroxetine.

Concomitant use of paroxetine with other drugs metabolized by cytochrome CYP2D6 has not been formally studied but may require lower doses than usually prescribed for either paroxetine or the other drug.

Therefore, coadministration of PEXEVA® (paroxetine mesylate) with other drugs that are metabolized by this isozyme, including certain drugs effective in the treatment of MDD (eg, nortriptyline, amitriptyline, imipramine, desipramine, and fluoxetine), phenothiazines, risperidone, and Type 1C antiarrhythmics (eg, propafenone, flecainide, and encainide), or that inhibit this enzyme (eg, quinidine), should be approached with caution.

However, due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, paroxetine, and thioridazine should not be coadministered (see CONTRAINDICATIONS and WARNINGS).

Tamoxifen is a pro-drug requiring metabolic activation by CYP2D6. Inhibition of CYP2D6 by paroxetine may lead to reduced plasma concentrations of an active metabolite (endoxifen) and hence reduced efficacy of tamoxifen (see PRECAUTIONS).

At steady state, when the CYP2D6 pathway is essentially saturated, paroxetine clearance is governed by alternative P450 isozymes, which, unlike CYP2D6, show no evidence of saturation (see PRECAUTIONS—Tricyclic Antidepressants).

Drugs Metabolized by Cytochrome CYP3A4: An in vivo interaction study involving the coadministration under steady-state conditions of paroxetine and terfenadine, a substrate for cytochrome CYP3A4, revealed no effect of paroxetine on terfenadine pharmacokinetics. In addition, in vitro studies have shown ketoconazole, a potent inhibitor of CYP3A4 activity, to be at least 100 times more potent than paroxetine as an inhibitor of the metabolism of several substrates for this enzyme, including terfenadine, astemizole, cisapride, triazolam, and cyclosporine. Based on the assumption that the relationship between paroxetine's in vitro K_i and its lack of effect on terfenadine's in vivo clearance predicts its effect on other 3A4 substrates, paroxetine's extent of inhibition of CYP3A4 activity is not likely to be of clinical significance.

Tricyclic Antidepressants (TCA): Caution is indicated in the coadministration of tricyclic antidepressants (TCAs) with PEXEVA® (paroxetine mesylate), because paroxetine may inhibit TCA metabolism. Plasma TCA concentrations may need to be monitored and the dose of TCA may need to be reduced, if a TCA is coadministered with PEXEVA® (paroxetine mesylate). (See PRECAUTIONS —Drugs Metabolized by Cytochrome CYP2D6).

Drugs Highly Bound to Plasma Protein: Because paroxetine is highly bound to plasma protein, administration of PEXEVA® (paroxetine mesylate) to a patient taking another drug that is highly protein-bound may cause increased free concentrations of the other drug, potentially resulting in adverse events. Conversely, adverse effects could result from displacement of paroxetine by other highly bound drugs.

Drugs That Interfere With Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin): Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs or SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when PEXEVA® (paroxetine mesylate) is initiated or discontinued.

Alcohol— Although paroxetine does not increase the impairment of mental and motor skills caused by alcohol, patients should be advised to avoid alcohol while taking PEXEVA® (paroxetine mesylate).

Lithium— A multiple-dose study has shown that there is no pharmacokinetic interaction between paroxetine and lithium carbonate. However, due to the potential for serotonin syndrome, the concurrent administration of paroxetine and lithium should be undertaken with caution.

Digoxin— The steady-state pharmacokinetics of paroxetine was not altered when administered with digoxin at steady state. Mean digoxin AUC at steady state decreased by 15% in the presence of paroxetine. Since there is little clinical experience, the concurrent administration of paroxetine and digoxin should be undertaken with caution.

Diazepam— Under steady-state conditions, diazepam does not appear to affect paroxetine kinetics. The effects of paroxetine on diazepam were not evaluated.

Procyclidine— Daily oral dosing of paroxetine (30 mg qd) increased steady-state AUC_{0-24}, C_{max}, and C_{min} values of procyclidine (5 mg oral qd) by 35%, 37%, and 67%, respectively, compared to procyclidine alone at steady state. If anticholinergic effects are seen, the dose of procyclidine should be reduced.

Beta-Blockers— In a study where propranolol (80 mg bid) was dosed orally for 18 days, the established steady-state plasma concentrations of propranolol were unaltered during coadministration with paroxetine (30 mg qd) for the final 10 days. The effects of propranolol on paroxetine have not been evaluated (see ADVERSE REACTIONS—Postmarketing Reports).

Theophylline— Reports of elevated theophylline levels associated with paroxetine treatment have been reported. While this interaction has not been formally studied, it is recommended that theophylline levels be monitored when these drugs are concurrently administered.

Fosamprenavir/Ritonavir— Coadministration of fosamprenavir/ ritonavir with paroxetine significantly decreased plasma levels of paroxetine. Any dose adjustment should be guided by clinical effect (tolerability and efficacy).

Electroconvulsive Therapy (ECT)— There are no clinical studies of the combined use of ECT and paroxetine.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Two-year carcinogenicity studies were conducted in rodents given paroxetine in the diet at 1, 5, and 25 mg/kg/day (mice) and 1, 5, and 20 mg/kg/day (rats). These doses are up to 2.4 (mouse) and 3.9 (rat) times the maximum recommended human dose (MRHD) for MDD and GAD on a mg/m2 basis. Because the MRHD for MDD is slightly less than that for OCD (50 mg vs 60 mg), the doses used in these carcinogenicity studies were only 2.0 (mouse) and 3.2 (rat) times the MRHD for OCD. There was a significantly greater number of male rats in the high-dose group with reticulum cell sarcomas (1/100, 0/50, 0/50, and 4/50 for control, low-, middle-, and high-dose groups, respectively) and a significantly increased linear trend across groups for the occurrence of lymphoreticular tumors in male rats. Female rats were not affected. Although there was a dose-related increase in the number of tumors in mice, there was no drug-related increase in the number of mice with tumors. The relevance of these findings to humans is unknown.

Mutagenesis: Paroxetine produced no genotoxic effects in a battery of 5 *in vitro* and 2 *in vivo* assays that included the following: bacterial mutation assay, mouse lymphoma mutation assay, unscheduled DNA synthesis assay, and tests for cytogenetic aberrations *in vivo* in mouse bone marrow and *in vitro* in human lymphocytes and in a dominant lethal test in rats.

Impairment of Fertility: Some clinical studies have shown that SSRIs (including paroxetine) may affect sperm quality during SSRI treatment, which may affect fertility in some men.

A reduced pregnancy rate was found in reproduction studies in rats at a dose of paroxetine of 15 mg/kg/day, which is 2.9 times the MRHD for MDD and GAD or 2.4 times the MRHD for OCD on a mg/m2 basis. Irreversible lesions occurred in the reproductive tract of male rats after dosing in toxicity studies for 2 to 52 weeks. These lesions consisted of vacuolation of epididymal tubular epithelium at 50 mg/kg/day and atrophic changes in the seminiferous tubules of the testes with arrested spermatogenesis at 25 mg/kg/day (9.8 and 4.9 times the MRHD for MDD and GAD; 8.2 and 4.1 times the MRHD for OCD and PD on a mg/m2 basis).

Pregnancy

Pregnancy Category D (see WARNINGS—Usage in Pregnancy: Teratogenic and Nonteratogenic Effects).

Labor and Delivery

The effect of paroxetine on labor and delivery in humans is unknown.

Nursing Mothers

Like many other drugs, paroxetine is secreted in human milk, and caution should be exercised when PEXEVA® (paroxetine mesylate) is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in the pediatric population have not been established (see BOX WARNING and WARNINGS—Clinical Worsening and Suicide Risk). Three placebo-controlled trials in 752 pediatric patients with MDD have been conducted with paroxetine, and the data were not sufficient to support a claim for use in pediatric patients. Anyone considering the use of paroxetine mesylate in a child or adolescent must balance the potential risks with the clinical need. Decreased appetite and weight loss have been observed in association with the use of SSRIs. Consequently, regular monitoring of weight and growth should be performed in children and adolescents treated with an SSRI such as PEXEVA®.

In placebo-controlled clinical trials conducted with pediatric patients, the following adverse events were reported in at least 2% of pediatric patients treated with paroxetine and occurred at a rate at least twice that for pediatric patients receiving placebo: emotional lability (including self-harm, suicidal thoughts, attempted suicide, crying, and mood fluctuations), hostility, decreased appetite, tremor, sweating, hyperkinesia, and agitation.

Events reported upon discontinuation of treatment with paroxetine in the pediatric clinical trials that included a taper phase regimen, which occurred in at least 2% of patients who received paroxetine and which occurred at a rate at least twice that of placebo, were: emotional lability (including suicidal ideation, suicide attempt, mood changes, and tearfulness), nervousness, dizziness, nausea, and abdominal pain (see Discontinuation of Treatment with Paroxetine).

Geriatric Use

SSRIs and SNRIs, including PEXEVA® (paroxetine mesylate), have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event (See PRECAUTIONS, Hyponatremia).

In worldwide premarketing paroxetine clinical trials, 17% of paroxetine-treated patients (approximately 700) were 65 years of age or older. Pharmacokinetic studies revealed a decreased clearance in the elderly, and a lower starting dose is recommended; there were, however, no overall differences in the adverse event profile between elderly and younger patients, and effectiveness was similar in younger and older patients (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Associated with Discontinuation of Treatment

Twenty percent (1199/6145) of patients treated with paroxetine in worldwide clinical trials in MDD and 11.8% (64/542), 9.4% (44/469), and 10.7% (79/735) of patients treated with paroxetine in worldwide trials in OCD, PD, and GAD, respectively, discontinued treatment due to an adverse event. The most common events (≥1%) associated with discontinuation and considered to be drug related (ie, those events associated with dropout at a rate approximately twice or greater for paroxetine compared to placebo) included the following:

	MDD		OCD		PD		GAD	
	Paroxetine	**Placebo**	**Paroxetine**	**Placebo**	**Paroxetine**	**Placebo**	**Paroxetine**	**Placebo**
CNS								
Somnolence	2.3%	0.7%	-	-	1.9%	0.3%	2.0%	0.2%
Insomnia	-	-	1.7%	0%	1.3%	0.3%	-	-
Agitation	1.1%	0.5%	-	-	-	-	-	-
Tremor	1.1%	0.3%	-					
Dizziness	-	-	1.5%	0%	-	-	1.0%	0.2%
Gastrointestinal								
Constipation	-	-	1.1%	0%	-	-	-	-
Nausea	3.2%	1.1%	1.9%	0%	3.2%	1.2%	2.0%	0.2%
Diarrhea	1.0%	0.3%	-	-	-	-	-	-
Dry mouth	1.0%	0.3%	-	-	-	-	-	-
Vomiting	1.0%	0.3%	-	-	-	-	-	-
Other								
Asthenia	1.6%	0.4%	1.9%	0.4%	-	-	1.8%	0.2%
Abnormal Ejaculation [1]	1.6%	0%	2.1%	0%	-	-	2.5%	0.5%
Sweating	1.0%	0.3%	-	-	-	-	1.1%	0.2%
Impotence [1]	-	-	1.5%	0%	-	-	-	-

Where numbers are not provided the incidence of the adverse events in patients treated with paroxetine was not >1% or was not greater than or equal to two times the incidence of placebo.

[1] Incidence corrected for gender.

Commonly Observed Adverse Events

Major Depressive Disorder

The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for paroxetine at least twice that for placebo, derived from Table 2 below) were: asthenia, sweating, nausea, decreased appetite, somnolence, dizziness, insomnia, tremor, nervousness, ejaculatory disturbance, and other male genital disorders.

Obsessive Compulsive Disorder

The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for paroxetine at least twice that of placebo, derived from Table 3 below) were: nausea, dry mouth, decreased appetite, constipation, dizziness, somnolence, tremor, sweating, impotence, and abnormal ejaculation.

Panic Disorder

The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for paroxetine at least twice that for placebo, derived from Table 3 below) were: asthenia, sweating, decreased appetite, libido decreased, tremor, abnormal ejaculation, female genital disorders, and impotence.

Generalized Anxiety Disorder

The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for paroxetine at least twice that for placebo, derived from Table 4) were: asthenia, infection, constipation, decreased appetite, dry mouth, nausea, libido decreased, somnolence, tremor, sweating, and abnormal ejaculation.

Incidence in Controlled Clinical Trials

The prescriber should be aware that the figures in the tables following cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the populations studied.

Major Depressive Disorder

Table 2 enumerates adverse events that occurred at an incidence of 1% or more among paroxetine-treated patients who participated in short-term (6-week) placebo-controlled trials in which patients were dosed in a range of 20 to 50 mg/day. Reported adverse events were classified using a standard COSTART-based Dictionary terminology.

TABLE 2

Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials for MDD[1]			
Body System	**Preferred Term**	**Paroxetine (n=421)**	**Placebo (n=421)**
Body as a Whole	Headache	18%	17%
	Asthenia	15%	6%
Cardiovascular	Palpitation	3%	1%
	Vasodilation	3%	1%
Dermatologic	Sweating	11%	2%
	Rash	2%	1%
Gastrointestinal	Nausea	26%	9%
	Dry Mouth	18%	12%
	Constipation	14%	9%
	Diarrhea	12%	8%
	Decreased Appetite	6%	2%
	Flatulence	4%	2%
	Oropharynx Disorder [2]	2%	0%
	Dyspepsia	2%	1%
Musculoskeletal	Myopathy	2%	1%
	Myalgia	2%	1%
	Myasthenia	1%	0%
Nervous System	Somnolence	23%	9%
	Dizziness	13%	6%
	Insomnia	13%	6%
	Tremor	8%	2%
	Nervousness	5%	3%
	Anxiety	5%	3%
	Paresthesia	4%	2%
	Libido Decreased	3%	0%
	Drugged Feeling	2%	1%
	Confusion	1%	0%
Respiration	Yawn	4%	0%
Special Senses	Blurred Vision	4%	1%
	Taste Perversion	2%	0%
Urogenital System	Ejaculatory Disturbance [3,4]	13%	0%
	Other Male Genital Disorders [3,5]	10%	0%
	Urinary Frequency	3%	1%
	Urination Disorder [6]	3%	0%
	Female Genital Disorders [3,7]	2%	0%

[1] Events reported by at least 1% of patients treated with paroxetine are included, except the following events which had an incidence on placebo ≥ paroxetine: abdominal pain, agitation, back pain, chest pain, CNS stimulation, fever, increased appetite, myoclonus, pharyngitis, postural hypotension, respiratory disorder (includes mostly “cold symptoms” or “URI”), trauma, and vomiting.

[2] Includes mostly “lump in throat” and “tightness in throat.”

[3] Percentage corrected for gender.

[4] Mostly “ejaculatory delay.”

[5] Includes “anorgasmia,” “erectile difficulties,” “delayed ejaculation/orgasm,” and “sexual dysfunction” and “impotence.”

[6] Includes mostly “difficulty with micturition” and “urinary hesitancy.”

[7] Includes mostly “anorgasmia” and “difficulty reaching climax/orgasm.”

Obsessive Compulsive Disorder and Panic Disorder

Table 3 enumerates adverse events that occurred at a frequency of 2% or more among OCD patients on paroxetine who participated in placebo-controlled trials of 12-weeks duration in which patients were dosed in a range of 20 to 60 mg/day or among patients with PD on paroxetine who participated in placebo-controlled trials of 10- to 12-weeks duration in which patients were dosed in a range of 10 to 60 mg/day.

TABLE 3

Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials for Obsessive Compulsive Disorder and Panic Disorder[1]

		Obsessive Compulsive Disorder		Panic Disorder	
Body System	**Preferred Term**	**Paroxetine (n=542)**	**Placebo (n=265)**	**Paroxetine (n=469)**	**Placebo (n=324)**
Body as a Whole	Asthenia	22%	14%	14%	5%
	Abdominal Pain	-	-	4%	3%
	Chest Pain	3%	2%	-	-
	Back Pain	-	-	3%	2%
	Chills	2%	1%	2%	1%
Cardiovascular	Vasodilation	4%	1%	-	-
	Palpitation	2%	0%	-	-
Dermatologic	Sweating	9%	3%	14%	6%
	Rash	3%	2%	-	-
Gastrointestinal	Nausea	23%	10%	23%	17%
	Dry Mouth	18%	9%	18%	11%
	Constipation	16%	6%	8%	5%
	Diarrhea	10%	10%	12%	7%
	Decreased Appetite	9%	3%	7%	3%
	Increased Appetite	4%	3%	2%	1%
Nervous System	Insomnia	24%	13%	18%	10%
	Somnolence	24%	7%	19%	11%
	Dizziness	12%	6%	14%	10%
	Tremor	11%	1%	9%	1%
	Nervousness	9%	8%	-	-
	Libido Decreased	7%	4%	9%	1%
	Agitation	-	-	5%	4%
	Anxiety	-	-	5%	4%
	Abnormal Dreams	4%	1%	-	-
	Concentration Impaired	3%	2%	-	-
	Depersonalization	3%	0%	-	-
	Myoclonus	3%	0%	3%	2%
	Amnesia	2%	1%	-	-
Respiratory	Rhinitis	-	-	3%	0%

System					
Special Senses	Abnormal Vision	4%	2%	-	-
	Taste Perversion	2%	0%	-	-
Urogenital System	Abnormal Ejaculation [2]	23%	1%	21%	1%
	Female Genital Disorder [2]	3%	0%	9%	1%
	Impotence [2]	8%	1%	5%	0%
	Urinary Frequency	3%	1%	2%	0%
	Urination Impaired	3%	0%	-	-
	Urinary Tract Infection	2%	1%	2%	1%

[1] Events reported by at least 2% of OCD or PD paroxetine-treated patients are included, except the following events which had an incidence on placebo ≥ paroxetine [OCD]: abdominal pain, agitation, anxiety, back pain, cough increased, depression, headache, hyperkinesia, infection, paresthesia, pharyngitis, respiratory disorder, rhinitis, and sinusitis. [PD]: abnormal dreams, abnormal vision, chest pain, cough increased, depersonalization, depression, dysmenorrhea, dyspepsia, flu syndrome, headache, infection, myalgia, nervousness, palpitation, paresthesia, pharyngitis, rash, respiratory disorder, sinusitis, taste perversion, trauma, urination impaired, and vasodilation.

[2] Percentage corrected for gender.

Generalized Anxiety Disorder

Table 4 enumerates adverse events that occurred at a frequency of 2% or more among GAD patients on paroxetine who participated in placebo-controlled trials of 8-weeks duration in which patients were dosed in a range of 10 mg/day to 50 mg/day.

TABLE 4

Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials for Generalized Anxiety Disorder[1]

Body System	Preferred Term	Paroxetine (n=735)	Placebo (n=529)
Body as a Whole	Asthenia	14%	6%
	Headache	17%	14%
	Infection	6%	3%
Cardiovascular	Vasodilation	3%	1%
Dermatologic	Sweating	6%	2%
Gastrointestinal	Nausea	20%	5%
	Dry Mouth	11%	5%
	Constipation	10%	2%
	Diarrhea	9%	7%
	Decreased Appetite	5%	1%
	Vomiting	3%	2%
Nervous System	Insomnia	11%	8%
	Somnolence	15%	5%
	Dizziness	6%	5%
	Tremor	5%	1%
	Nervousness	4%	3%
	Libido Decreased	9%	2%
Respiratory System	Respiratory Disorder	7%	5%
	Sinusitis	4%	3%
	Yawn	4%	-
Special Senses	Abnormal Vision	2%	1%
Urogenital System	Abnormal Ejaculation [2]	25%	2%
	Female Genital Disorder [2]	4%	1%
	Impotence [2]	4%	3%

[1] Events reported by at least 2% of GAD patients treated with paroxetine are included, except the following events which had an incidence on placebo ≥ paroxetine: abdominal pain, back pain, trauma, dyspepsia, myalgia, and pharyngitis.

[2] Percentage corrected for gender.

Dose Dependency of Adverse Events: A comparison of adverse event rates in a fixed-dose study comparing paroxetine 10, 20, 30, and 40 mg/day with placebo in the treatment of MDD revealed a clear dose dependency for some of the more common adverse events associated with paroxetine use, as shown in the following table:

TABLE 5

Treatment-Emergent Adverse Experience Incidence in a Dose-Comparison Trial in the Treatment of MDD*

Body System/ Preferred Term	**Placebo**	**Paroxetine**			
	n=51	**10 mg n=102**	**20 mg n=104**	**30 mg n=101**	**40 mg n=102**
Body as a Whole					
Asthenia	0.0%	2.9%	10.6%	13.9%	12.7%
Dermatology					
Sweating	2.0%	1.0%	6.7%	8.9%	11.8%
Gastrointestinal					
Constipation	5.9%	4.9%	7.7%	9.9%	12.7%
Decreased Appetite	2.0%	2.0%	5.8%	4.0%	4.9%
Diarrhea	7.8%	9.8%	19.2%	7.9%	14.7%
Dry Mouth	2.0%	10.8%	18.3%	15.8%	20.6%
Nausea	13.7%	14.7%	26.9%	34.7%	36.3%
Nervous System					
Anxiety	0.0%	2.0%	5.8%	5.9%	5.9%
Dizziness	3.9%	6.9%	6.7%	8.9%	12.7%
Nervousness	0.0%	5.9%	5.8%	4.0%	2.9%
Paresthesia	0.0%	2.9%	1.0%	5.0%	5.9%
Somnolence	7.8%	12.7%	18.3%	20.8%	21.6%
Tremor	0.0%	0.0%	7.7%	7.9%	14.7%
Special Senses					
Blurred Vision	2.0%	2.9%	2.9%	2.0%	7.8%
Urogenital System					
Abnormal Ejaculation	0.0%	5.8%	6.5%	10.6%	13.0%
Impotence	0.0%	1.9%	4.3%	6.4%	1.9%
Male Genital Disorders	0.0%	3.8	8.7%	6.4%	3.7%

*Rule for including adverse events in table: incidence at least 5% for one of paroxetine groups and ≥ twice the placebo incidence for at least one paroxetine group.

In a fixed-dose study comparing placebo and paroxetine 20, 40, and 60 mg in the treatment of OCD, there was no clear relationship between adverse events and the dose of paroxetine to which patients were assigned. No new adverse events were observed in the paroxetine 60 mg dose group compared to any of the other treatment groups.

In a fixed-dose study comparing placebo and paroxetine 10, 20, and 40 mg in the treatment of PD, there was no clear relationship between adverse events and the dose of paroxetine to which patients were assigned, except for asthenia, dry mouth, anxiety, libido decreased, tremor, and abnormal ejaculation. In flexible-dose studies, no new adverse events were observed in patients receiving 60 mg of paroxetine compared to any of the other treatment groups.

In a fixed-dose study comparing placebo and 20 and 40 mg of paroxetine in the treatment of GAD, for most of the adverse events, there was no clear relationship between adverse events and the dose of paroxetine to which patients were assigned, except for the following adverse events: asthenia, constipation, and abnormal ejaculation.

In flexible dose studies, no new adverse events were observed in patients receiving paroxetine 60 mg compared to any of the other treatment groups.

Adaptation to Certain Adverse Events: Over a 4- to 6-week period, there was evidence of adaptation to some adverse events with continued therapy (eg, nausea and dizziness), but less to other effects (eg, dry mouth, somnolence, and asthenia).

Male and Female Sexual Dysfunction with SSRIs: Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences.

Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence.

In placebo-controlled clinical trials involving more than 3200 patients the ranges for the reported incidence of sexual side effects in males and females with MDD, OCD, PD, social anxiety disorder, GAD, and post traumatic stress disorder (PTSD) are displayed in Table 6 .

TABLE 6

Incidence of Sexual Adverse Events in Controlled Clinical Trials		
	Paroxetine	**Placebo**
n (males)	**1446**	**1042**
Decreased Libido	6% - 15%	0% - 5%
Ejaculatory Disturbance	13% - 28%	0% - 2%
Impotence	2% - 9%	0% - 3%
n (females)	**1822**	**1340**
Decreased Libido	0% - 9%	0% - 2%
Orgasmic Disturbance	2% - 9%	0% - 1%

There are no adequate and well-controlled studies examining sexual dysfunction with paroxetine treatment.

Paroxetine treatment has been associated with several cases of priapism. In those cases with a known outcome, patients recovered without sequelae.

While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.

Weight and Vital Sign Changes: Significant weight loss may be an undesirable result of treatment with paroxetine for some patients but, on average, patients in controlled trials had minimal (about 1 pound) weight loss vs smaller changes on placebo and active control. No significant changes in vital signs (systolic and diastolic blood pressure, pulse, and temperature) were observed in patients treated with paroxetine in controlled clinical trials.

ECG Changes: In an analysis of ECGs obtained in 682 patients treated with paroxetine and 415 patients treated with placebo in controlled clinical trials, no clinically significant changes were seen in the ECGs of either group.

Liver Function Tests: In placebo-controlled clinical trials, patients treated with paroxetine exhibited abnormal values on liver function tests at no greater rate than that seen in placebo-treated patients. In particular, the paroxetine vs placebo comparisons for alkaline phosphatase, SGOT, SGPT, and bilirubin revealed no differences in the percentage of patients with marked abnormalities.

Hallucinations: In pooled clinical trials of immediate-release paroxetine hydrochloride, hallucinations were observed in 22 of 9089 patients receiving drug and 4 of 3187 patients receiving placebo.

Other Events Observed During the Premarketing Evaluation of Paroxetine

During its premarketing assessment in MDD, multiple doses of paroxetine were administered to 6145 patients in phase 2 and 3 studies. The conditions and duration of exposure to paroxetine varied greatly and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, and fixed-dose and titration studies. During

premarketing clinical trials in OCD, PD, and GAD, 542, 469, and 735 patients, respectively, received multiple doses of paroxetine. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, reported adverse events were classified using a standard COSTART-based Dictionary terminology. The frequencies presented, therefore, represent the proportion of the 9089 patients exposed to multiple doses of paroxetine who experienced an event of the type cited on at least one occasion while receiving paroxetine. All reported events are included except those already listed in Tables 2 to 4 , those reported in terms so general as to be uninformative, and those events where a drug cause was remote.

It is important to emphasize that although the events reported occurred during treatment with paroxetine, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Events of major clinical importance are also described in the PRECAUTIONS section.

Body as a Whole: *infrequent* : allergic reaction, chills, face edema, malaise, neck pain; rare: adrenergic syndrome, cellulitis, moniliasis, neck rigidity, pelvic pain, peritonitis, sepsis, ulcer. ***Cardiovascular System:*** frequent: hypertension, tachycardia; *infrequent* : bradycardia, hematoma, hypotension, migraine, postural hypotension, syncope; *rare:* angina pectoris, arrhythmia nodal, atrial fibrillation, bundle branch block, cerebral ischemia, cerebrovascular accident, congestive heart failure, heart block, low cardiac output, myocardial infarction, myocardial ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombophlebitis, thrombosis, varicose vein, vascular headache, ventricular extrasystoles. ***Digestive System:*** *infrequent:* bruxism, colitis, dysphagia, eructation, gastritis, gastroenteritis, gingivitis, glossitis, increased salivation, liver function tests abnormal, rectal hemorrhage, ulcerative stomatitis; *rare:* aphthous stomatitis, bloody diarrhea, bulimia, cardiospasm, chlolelithiasis, duodenitis, enteritis, esophagitis, fecal impactions, fecal incontinence, gum hemorrhage, hematemesis, hepatitis, ileitis, ileus, intestinal obstruction, jaundice, melena, mouth ulceration, peptic ulcer, salivary gland enlargement, sialadenitis, stomach ulcer, stomatitis, tongue discoloration, tongue edema, tooth caries. ***Endocrine System:*** *rare:* diabetes mellitus, goiter, hyperthyroidism, hypothyroidism, thyroiditis. ***Hemic and Lymphatic Systems:*** *infrequent:* anemia, leukopenia, lymphadenopathy, purpura; *rare:* abnormal erythrocytes, basophilia, bleeding time increased, eosinophilia, hypochromic anemia, iron deficiency anemia, leukocytosis, lymphedema, abnormal lymphocytes, lymphocytosis, microcytic anemia, monocytosis, normocytic anemia, thrombocythemia, thrombocytopenia. ***Metabolic and Nutritional:*** *frequent* : weight gain; *infrequent:* edema, peripheral edema, SGOT increased, SGPT increased, thirst, weight loss; *rare:* alkaline phosphatase increased, bilirubinemia, BUN increased, creatinine phosphokinase increased, dehydration, gamma globulins increased, gout, hypercalcemia, hypercholesteremia, hyperglycemia, hyperkalemia, hyperphosphatemia, hypocalcemia, hypoglycemia, hypokalemia, hyponatremia, ketosis, lactic dehydrogenase increased, non-protein nitrogen (NPN) increased. ***Musculoskeletal System:*** *frequent:* arthralgia; *infrequent:* arthritis, arthrosis; *rare:* bursitis, myositis, osteoporosis, generalized spasm, tenosynovitis, tetany. ***Nervous System:*** *frequent:* emotional lability, vertigo; *infrequent:* abnormal thinking, alcohol abuse, ataxia, dystonia, dyskinesia, euphoria, hallucinations, hostility, hypertonia, hypesthesia, hypokinesia, incoordination, lack of emotion, libido increased, manic reaction, neurosis, paralysis, paranoid reaction; *rare:* abnormal gait, akinesia, antisocial reaction, aphasia, choreoathetosis, circumoral paresthesias, convulsion, delirium, delusions, diplopia, drug dependence, dysarthria, extrapyramidal syndrome, fasciculations, grand mal convulsion, hyperalgesia, hysteria, manic-depressive reaction, meningitis, myelitis, neuralgia, neuropathy, nystagmus, peripheral neuritis, psychotic depression, psychosis, reflexes decreased, reflexes increased, stupor, torticollis, trismus, withdrawal syndrome. ***Respiratory System:*** *infrequent:* asthma, bronchitis, dyspnea, epistaxis, hyperventilation, pneumonia, respiratory flu; *rare:* emphysema, hemoptysis, hiccups, lung fibrosis, pulmonary edema, sputum increased, stridor, voice alteration. ***Skin and Appendages:*** *frequent:* pruritus; *infrequent:* acne, alopecia, contact dermatitis, dry skin, ecchymosis, eczema, herpes simplex, photosensitivity, urticaria; *rare:* angioedema, erythema nodosum, erythema multiforme, exfoliative dermatitis, fungal dermatitis, furunculosis, herpes zoster, hirsutism, maculopapular rash, seborrhea, skin discoloration, skin hypertrophy, skin ulcer, sweating decreased, vesiculobullous rash. ***Special Senses:*** *frequent:* tinnitus; *infrequent:* abnormality of accommodation, conjunctivitis, ear pain, eye pain, keratoconjunctivitis, mydriasis, otitis media; *rare:* amblyopia, anisocoria, blepharitis, cataract, conjunctival edema, corneal ulcer, deafness, exophthalmos, eye hemorrhage, glaucoma, hyperacusis, night blindness, otitis externa, parosmia, photophobia, ptosis, retinal hemorrhage, taste loss, visual field defect. ***Urogenital System:*** *infrequent:* amenorrhea, breast pain, cystitis, dysuria, hematuria, menorrhagia, nocturia, pyuria, polyuria, urinary incontinence, urinary retention, urinary urgency, vaginitis; *rare:* abortion, breast atrophy, breast enlargement, endometrial disorder, epididymitis, female lactation, fibrocystic breast, kidney calculus, kidney pain, leukorrhea, mastitis, metrorrhagia, nephritis, oliguria, salpingitis, urethritis, urinary casts, uterine spasm, urolith, vaginal hemorrhage, vaginal moniliasis.

Postmarketing Reports

Voluntary reports of adverse events in patients taking paroxetine that have been received since market introduction and not listed above that may have no causal relationship with the drug include acute pancreatitis, elevated liver function tests (the most severe cases were deaths due to liver necrosis, and grossly elevated transaminases associated with severe liver dysfunction), Guillain-

Barré syndrome, Stevens-Johnson syndrome, toxic epidermal necrolysis, priapism, syndrome of inappropriate ADH secretion, symptoms suggestive of prolactinemia and galactorrhea; extrapyramidal symptoms which have included akathisia, bradykinesia, cogwheel rigidity, dystonia, hypertonia, oculogyric crisis which has been associated with concomitant use of pimozide, tremor and trismus; status epilepticus, acute renal failure, pulmonary hypertension, allergic alveolitis, anaphylaxis, eclampsia, laryngismus, optic neuritis, porphyria, restless legs syndrome (RLS), ventricular fibrillation, ventricular tachycardia (including torsade de pointes), thrombocytopenia, hemolytic anemia, events related to impaired hematopoiesis (including aplastic anemia, pancytopenia, bone marrow aplasia, and agranulocytosis), and vasculitic syndromes (such as Henoch-Schönlein purpura), and premature births in pregnant women.

There has been a case report of an elevated phenytoin level after 4 weeks of paroxetine and phenytoin coadministration. There has been a case report of severe hypotension when paroxetine was added to chronic metoprolol treatment.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: Paroxetine is not a controlled substance.

Physical and Psychologic Dependence: Paroxetine has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for history of drug abuse, and such patients should be observed closely for signs of PEXEVA® (paroxetine mesylate) misuse or abuse (eg, development of tolerance, incrementations of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience: Since the introduction of paroxetine in the US, 342 spontaneous cases of deliberate or accidental overdosage during paroxetine treatment have been reported worldwide (circa 1999). These include overdoses with paroxetine alone and in combination with other substances. Of these, 48 cases were fatal and, of the fatalities, 17 appeared to involve paroxetine alone. Eight fatal cases which documented the amount of paroxetine ingested were generally confounded by the ingestion of other drugs or alcohol or the presence of significant comorbid conditions. Of 145 non-fatal cases with known outcome, most recovered without sequelae. The largest known ingestion involved 2000 mg of paroxetine (33 times the maximum recommended daily dose) in a patient who recovered.

Commonly reported adverse events associated with paroxetine overdosage include somnolence, coma, nausea, tremor, tachycardia, confusion, vomiting, and dizziness. Other notable signs and symptoms observed with overdoses involving paroxetine (alone or with other substances) include mydriasis, convulsions (including status epilepticus), ventricular dysrhythmias (including torsade de pointes), hypertension, aggressive reactions, syncope, hypotension, stupor, bradycardia, dystonia, rhabdomyolysis, symptoms of hepatic dysfunction (including hepatic failure, hepatic necrosis, jaundice, hepatitis, and hepatic steatosis), serotonin syndrome, manic reactions, myoclonus, acute renal failure, and urinary retention.

Overdosage Management: No specific antidotes for paroxetine are known. Treatment should consist of those general measures employed in the management of overdosage with any drugs effective in the treatment of MDD.

Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended.

Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit.

A specific caution involves patients who are taking or have recently taken paroxetine who might ingest excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the parent tricyclic and/or an active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation (see Drugs Metabolized by Cytochrome CYP2D6 under PRECAUTIONS).

In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference* (PDR).

DOSAGE AND ADMINISTRATION

Major Depressive Disorder

Usual Initial Dosage: PEXEVA® (paroxetine mesylate) should be administered as a single daily dose with or without food, usually in the morning. The recommended initial dose is 20 mg/day. Patients were dosed in a range of 20 to 50 mg/day in the clinical trials demonstrating the effectiveness of paroxetine in the treatment of MDD. As with all drugs effective in the treatment of MDD, the full effect may be delayed. Some patients not responding to a 20 mg dose may benefit from dose increases, in 10 mg/day increments, up to a maximum of 50 mg/day. Dose changes should occur at intervals of at least 1 week.

Maintenance Therapy: There is no body of evidence available to answer the question of how long the patient treated with paroxetine should remain on it. It is generally agreed that acute episodes of MDD require several months or longer of sustained pharmacologic therapy. Whether the dose needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

Systematic evaluation of the efficacy of paroxetine has shown that efficacy is maintained for periods of up to 1 year with doses that averaged about 30 mg.

Obsessive Compulsive Disorder
Usual Initial Dosage: PEXEVA® (paroxetine mesylate) should be administered as a single daily dose with or without food, usually in the morning. The recommended dose of paroxetine in the treatment of OCD is 40 mg daily. Patients should be started on 20 mg/day and the dose can be increased in 10 mg/day increments. Dose changes should occur at intervals of at least 1 week. Patients were dosed in a range of 20 to 60 mg/day in the clinical trials demonstrating the effectiveness of paroxetine in the treatment of OCD. The maximum dosage should not exceed 60 mg/day.

Maintenance Therapy: Long-term maintenance of efficacy was demonstrated in a 6-month relapse prevention trial. In this trial, patients with OCD assigned to paroxetine demonstrated a lower relapse rate compared to patients on placebo (see CLINICAL PHARMACOLOGY). OCD is a chronic condition, and it is reasonable to consider continuation for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

Panic Disorder
Usual Initial Dosage: PEXEVA® (paroxetine mesylate) should be administered as a single daily dose with or without food, usually in the morning. The target dose of paroxetine in the treatment of PD is 40 mg/day. Patients should be started on 10 mg/day. Dose changes should occur in 10 mg/day increments and at intervals of at least 1 week. Patients were dosed in a range of 10 to 60 mg/day in the clinical trials demonstrating the effectiveness of paroxetine. The maximum dosage should not exceed 60 mg/day.

Maintenance Therapy: Long-term maintenance of efficacy was demonstrated in a 3-month relapse prevention trial. In this trial, patients with PD assigned to paroxetine demonstrated a lower relapse rate compared to patients on placebo (see CLINICAL PHARMACOLOGY). PD is a chronic condition, and it is reasonable to consider continuation for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

Generalized Anxiety Disorder
Usual Initial Dosage: PEXEVA® (paroxetine mesylate) should be administered as a single daily dose with or without food, usually in the morning. In clinical trials the effectiveness of paroxetine was demonstrated in patients dosed in a range of 20 to 50 mg/day. The recommended starting dosage and the established effective dosage is 20 mg/day. There is not sufficient evidence to suggest a greater benefit to doses higher than 20 mg/day. Dose changes should occur in 10 mg/day increments and at intervals of at least 1 week.

Maintenance Therapy: Systematic evaluation of continuing paroxetine for periods of up to 24 weeks in patients with GAD who had responded while taking paroxetine during an 8-week acute treatment phase has demonstrated a benefit of such maintenance (see CLINICAL PHARMACOLOGY—Clinical Trials). Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment.

Special Populations
Treatment of Pregnant Women During the Third Trimester: Neonates exposed to paroxetine and other SSRIs or SNRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see PRECAUTIONS). When treating pregnant women with paroxetine during the third trimester, the physician should carefully consider the potential risks and benefits of treatment.

Dosage for Elderly or Debilitated, and Patients with Severe Renal or Hepatic Impairment : The recommended initial dose is 10 mg/day for elderly patients, debilitated patients, and/or patients with severe renal or hepatic impairment. Increases may be made if indicated. Dosage should not exceed 40 mg/day.

Switching a Patient To or From a Monoamine Oxidase Inhibitor (MAOI) Intended to Treat Psychiatric Disorders:
At least 14 days should elapse between discontinuation of an MAOI intended to treat psychiatric disorders and initiation of therapy with PEXEVA®. Conversely, at least 14 days should be allowed after stopping PEXEVA® before starting an MAOI intended to treat psychiatric disorders (see CONTRAINDICATIONS).

Use of PEXEVA® With Other MAOIs, Such as Linezolid or Methylene Blue:
Do not start PEXEVA® in a patient who is being treated with linezolid or intravenous methylene blue because there is increased risk of serotonin syndrome. In a patient who requires more urgent treatment of a psychiatric condition, other interventions, including hospitalization, should be considered (see CONTRAINDICATIONS).

In some cases, a patient already receiving PEXEVA® therapy may require urgent treatment with linezolid or intravenous methylene blue. If acceptable alternatives to linezolid or intravenous methylene blue treatment are not available and the potential benefits of

linezolid or intravenous methylene blue treatment are judged to outweigh the risks of serotonin syndrome in a particular patient, PEXEVA® should be stopped promptly, and linezolid or intravenous methylene blue can be administered. The patient should be monitored for symptoms of serotonin syndrome for 2 weeks or until 24 hours after the last dose of linezolid or intravenous methylene blue, whichever comes first. Therapy with PEXEVA® may be resumed 24 hours after the last dose of linezolid or intravenous methylene blue (see WARNINGS).

The risk of administering methylene blue by non-intravenous routes (such as oral tablets or by local injection) or in intravenous doses much lower than 1 mg/kg with PEXEVA® is unclear. The clinician should, nevertheless, be aware of the possibility of emergent symptoms of serotonin syndrome with such use (see WARNINGS).

Discontinuation of Treatment with PEXEVA® (paroxetine mesylate): Symptoms associated with discontinuation of paroxetine have been reported (see PRECAUTIONS). Patients should be monitored for these symptoms when discontinuing treatment, regardless of the indication for which paroxetine is being prescribed. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

HOW SUPPLIED

Tablets:
Film-coated, modified-oval tablets as follows:
10 mg white tablets with the inscription POT 10 on one side.
NDC 68968-2010-1 Bottles of 30

20 mg dark orange tablets with the inscription POT 20 on one side.
The tablets are scored on both sides.
NDC 68968-2020-1 Bottles of 30

30 mg yellow tablets with the inscription POT 30 on one side.
NDC 68968-2030-1 Bottles of 30

40 mg rose tablets with the inscription POT 40 on one side.
NDC 68968-2040-1 Bottles of 30

Protect from Humidity. Store at 25°C (77°F); excursions permitted to 15°-30°C (59° and 86°F) (see USP Controlled Room Temperature)
PI-2000-15
DATE OF ISSUANCE: 12/2012
Noven Therapeutics, LLC
Miami, FL 33186

Rx only

MEDICATION GUIDE
PEXEVA® (pex-EE-va)
(paroxetine mesylate)
Read the Medication Guide that comes with PEXEVA® before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment. Talk with your healthcare provider if there is something you do not understand or want to learn more about.
What is the most important information I should know about PEXEVA®?
PEXEVA® and other antidepressant medicines may cause serious side effects, including:
1. Suicidal thoughts or actions:

- **PEXEVA® and other antidepressant medicines may increase suicidal thoughts or actions** in some children, teenagers, or young adults within the **first few months of treatment or when the dose is changed.**
- Depression or other serious mental illnesses are the most important causes of suicidal thoughts or actions.
- Watch for these changes and call your healthcare provider right away if you notice:
- New or sudden changes in mood, behavior, actions, thoughts, or feelings, especially if severe.
- Pay particular attention to such changes when PEXEVA® is started or when the dose is changed.

Keep all follow-up visits with your healthcare provider and call between visits if you are worried about symptoms.

Call your healthcare provider right away if you have any of the following symptoms, or call 911 if an emergency, especially if they are new, worse, or worry you:

- attempts to commit suicide
- acting on dangerous impulses
- acting aggressive or violent
- thoughts about suicide or dying
- new or worse depression
- new or worse anxiety or panic attacks
- feeling agitated, restless, angry or irritable
- trouble sleeping
- an increase in activity or talking more than what is normal for you
- other unusual changes in behavior or mood

Call your healthcare provider right away if you have any of the following symptoms, or call 911 if an emergency. PEXEVA® may be associated with these serious side effects:

2. Serotonin Syndrome. This condition can be life-threatening and may include:

- agitation, hallucinations, coma or other changes in mental status
- coordination problems or muscle twitching (overactive reflexes)
- racing heartbeat, high or low blood pressure
- sweating or fever
- nausea, vomiting, or diarrhea
- muscle rigidity

3. Severe allergic reactions:

- trouble breathing
- swelling of the face, tongue, eyes or mouth
- rash, itchy welts (hives) or blisters, alone or with fever or joint pain

4. Abnormal bleeding: PEXEVA® and other antidepressant medicines may increase your risk of bleeding or bruising, especially if you take the blood thinner warfarin (Coumadin®, Jantoven®), a non-steroidal anti-inflammatory drug (NSAID's, like ibuprofen or naproxen), or aspirin.

5. Seizures or convulsions

6. Manic episodes:

- greatly increased energy
- severe trouble sleeping
- racing thoughts
- reckless behavior
- unusually grand ideas
- excessive happiness or irritability
- talking more or faster than usual

7. Changes in appetite or weight. Children and adolescents should have height and weight monitored during treatment.

8. Low salt (sodium) levels in the blood. Elderly people may be at greater risk for this. Symptoms may include:

- headache
- weakness or feeling unsteady
- confusion, problems concentrating or thinking or memory problems

Do not stop PEXEVA® without first talking to your healthcare provider. Stopping PEXEVA® too quickly may cause serious symptoms including:

- anxiety, irritability, high or low mood, feeling restless or changes in sleep habits
- headache, sweating, nausea, dizziness
- electric shock-like sensations, shaking, confusion

What is PEXEVA®?

PEXEVA® is a prescription medicine used to treat depression. It is important to talk with your healthcare provider about the risks of treating depression and also the risks of not treating it. You should discuss all treatment choices with your healthcare provider.

PEXEVA® is also used to treat:

- Major Depressive Disorder (MDD)
- Obsessive Compulsive Disorder (OCD)
- Panic Disorder
- Generalized Anxiety Disorder (GAD)

Talk to your healthcare provider if you do not think that your condition is getting better with PEXEVA® treatment.

Who should not take PEXEVA®?

Do not take PEXEVA® if you:

- are allergic to paroxetine mesylate or any of the ingredients in PEXEVA®. See the end of this Medication Guide for a complete list of ingredients in PEXEVA®.
- take a Monoamine Oxidase Inhibitor (MAOI). Ask your healthcare provider or pharmacist if you are not sure if you take an MAOI.
- Do not take an MAOI within 2 weeks of stopping PEXEVA® unless directed to do so by your physician.
- Do not start PEXEVA® if you stopped taking an MAOI in the last 2 weeks unless directed to do so by your physician.
- **People who take PEXEVA® close in time to an MAOI may have serious or even life-threatening side effects. Get medical help right away if you have any of these symptoms:**
- high fever
- uncontrolled muscle spasms
- stiff muscles
- rapid changes in heart rate or blood pressure
- confusion
- loss of consciousness (pass out)
- **take Mellaril® (thioridazine). Do not take Mellaril® together with PEXEVA® because this can cause serious heart rhythm problems or sudden death.**
- **take the antipsychotic medicine pimozide (Orap®) because this can cause serious heart problems.**

What should I tell my healthcare provider before taking PEXEVA®? Ask if you are not sure.

Before starting PEXEVA®, tell your healthcare provider if you:

- are pregnant, may be pregnant, or plan to become pregnant. There is a possibility that PEXEVA® may harm your unborn baby, including an increased risk of birth defects, particularly heart defects. Other risks include a serious condition in which there is not enough oxygen in the baby's blood. Your baby may also have certain other symptoms shortly after birth. Premature births have also been reported in some women who used PEXEVA® during pregnancy.
- are breastfeeding. PEXEVA® passes into your milk. Talk to your healthcare provider about the best way to feed your baby while taking PEXEVA®.
- are taking certain drugs such as:
- triptans used to treat migraine headache
- other antidepressants (SSRI's, SNRI's, tricyclics, or lithium) or antipsychotics
- drugs that affect serotonin such as lithium, tramadol, tryptophan, St. John's wort
- certain drugs used to treat irregular heart beats
- certain drugs used to treat schizophrenia
- certain drugs used to treat HIV infection
- certain drugs that affect the blood such as warfarin, aspirin, and ibuprofen
- certain drugs used to treat epilepsy
- atomoxetine
- cimetidine
- fentanyl
- metoprolol
- pimozide
- procyclidine
- tamoxifen
- have liver problems
- have kidney problems
- have heart problems
- have or had seizures or convulsions
- have bipolar disorder or mania
- have low sodium levels in your blood
- have a history of a stroke
- have high blood pressure
- have or had bleeding problems
- have glaucoma (high pressure in the eye).

Tell your healthcare provider about all the medicines **that you take,** including prescription and non-prescription medicines, vitamins, and herbal supplements. PEXEVA® and some medicines may interact with each other, may not work as well, or may cause serious side effects.

Your healthcare provider or pharmacist can tell you if it is safe to take PEXEVA® with your other medicines. Do not start or stop any medicine while taking PEXEVA® without talking to your healthcare provider first.

If you take PEXEVA®, you should not take any other medicines that contain paroxetine including: PAXIL® and PAXIL CR®.

How should I take PEXEVA®?

- Take PEXEVA® exactly as prescribed. Your healthcare provider may need to change the dose of PEXEVA® until it is the right dose for you.
- PEXEVA® may be taken with or without food.
- If you miss a dose of PEXEVA®, take the missed dose as soon as you remember. If it is almost time for the next dose, skip the missed dose and take your next dose at the regular time. Do not take two doses of PEXEVA® at the same time.
- If you take too much PEXEVA®, call your healthcare provider or poison control center right away, or get emergency treatment.
- Do not stop taking PEXEVA® suddenly without talking to your doctor (unless you have symptoms of a severe allergic reaction). If you need to stop taking PEXEVA®, your healthcare provider can tell you how to safely stop taking it.

What should I avoid while taking PEXEVA®?

PEXEVA® can cause sleepiness or may affect your ability to make decisions, think clearly, or react quickly. You should not drive, operate heavy machinery, or do other dangerous activities until you know how PEXEVA® affects you. Do not drink alcohol while using PEXEVA®.

What are the possible side effects of PEXEVA®?

PEXEVA® may cause serious side effects, including all of those described in the section entitled “What is the most important information I should know about PEXEVA®?”

Common possible side effects in people who take PEXEVA® include:

- Nausea
- Sleepiness
- Weakness
- Dizziness
- Feeling anxious
- Trouble sleeping
- Sexual problems
- Sweating
- Shaking
- Not feeling hungry
- Dry mouth
- Constipation
- Infection
- Yawning

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of PEXEVA®. For more information, ask your healthcare provider or pharmacist.

CALL YOUR DOCTOR FOR MEDICAL ADVICE ABOUT SIDE EFFECTS. YOU MAY REPORT SIDE EFFECTS TO THE FDA AT 1-800-FDA-1088.

How should I store PEXEVA®?

- Store PEXEVA® at room temperature between 59°F and 86°F (15°C to 30°C).
- Keep PEXEVA® away from light.
- Keep PEXEVA® bottle closed tightly.

Keep PEXEVA® and all medicines out of the reach of children.

General information about PEXEVA®

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use PEXEVA® for a condition for which it was not prescribed. Do not give PEXEVA® to other people, even if they have the same condition. It may harm them.

This Medication Guide summarizes the most important information about PEXEVA®. If you would like more information, talk with your healthcare provider. You may ask your healthcare provider or pharmacist for information about PEXEVA® that is written for healthcare professionals.

For more information about PEXEVA® call (**1–800-455-8070**) or go to www.PEXEVA.com.

What are the ingredients in PEXEVA®?

Active ingredient: paroxetine mesylate

Inactive ingredients: dibasic calcium phosphate, hydroxypropyl methylcellulose, hydroxypropylcellulose, magnesium stearate, sodium starch glycolate, titanium dioxide, and iron oxide(s)

Manufactured by:
Norwich Pharmaceuticals, Inc.
Norwich, NY 13815

Distributed by:
Noven Therapeutics, LLC, 11960 SW 144 St., Miami, FL 33186

Revised 12/2012

This Medication Guide has been approved by the U.S. Food and Drug Administration.

PACKAGE LABEL – PRINCIPAL DISPLAY PANEL – 10 MG LABEL
NDC 68968-2010-1
30 Tablets
PEXEVA®
(paroxetine mesylate)
Tablets
Equivalent to 10 mg paroxetine base
10 mg
Rx only
NOVEN THERAPEUTICS, LLC

PACKAGE LABEL – PRINCIPAL DISPLAY PANEL – 20 MG LABEL
NDC 68968-2020-1
30 Tablets
PEXEVA®
(paroxetine mesylate)
Delayed-Release Tablets
Equivalent to 20 mg paroxetine base
20 mg
Rx only
NOVEN THERAPEUTICS, LLC

PACKAGE LABEL – PRINCIPAL DISPLAY PANEL – 30 MG LABEL
NDC 68968-2030-1
30 Tablets
PEXEVA®
(paroxetine mesylate)
Delayed-Release Tablets
Equivalent to 30 mg paroxetine base
30 mg
Rx only
NOVEN THERAPEUTICS, LLC

PACKAGE LABEL – PRINCIPAL DISPLAY PANEL – 40 MG LABEL
NDC 68968-2040-1
30 Tablets
PEXEVA®
(paroxetine mesylate)
Delayed-Release Tablets

Equivalent to 40 mg paroxetine base
40 mg
Rx only
NOVEN THERAPEUTICS, LLC

Revised: 12/2012

Distributed by: NOVEN THERAPEUTICS, LLC

Guidance for Industry

Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms — Recommendations for Clinical Evaluation

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions on the content of the draft document contact Margaret Kober at 301-827-4243

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

January 2003
Clinical/Medical

Guidance for Industry

Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms — Recommendations for Clinical Evaluation

Additional copies are available from:

The Division of Drug Information (HFD-240)
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573
Internet at http://www.fda.gov/cder/guidance/index.htm

U.S. Department of Health and Human Services
Food and Drug Administration
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Guidance for Industry[1]

Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms — Recommendations for Clinical Evaluation

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

I. INTRODUCTION

This guidance updates the final guidance *Guidance for Clinical Evaluation of Combination Estrogen/Progestin - Containing Drug Products Used for Hormone Replacement Therapy of Postmenopausal Women,* published in March 1995. The guidance is intended to provide recommendations to industry for studies of estrogen and estrogen/progestin drug products for the treatment of moderate to severe vasomotor symptoms associated with the menopause and moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. The guidance also addresses the reduction of the risk of endometrial hyperplasia or adenocarcinoma from estrogen exposure in postmenopausal women who have a uterus. For other indications, such as prevention of osteoporosis, sponsors are asked to direct inquiries to the appropriate CDER Office of New Drugs review division.[2]

II. BACKGROUND

Estrogen therapy has been used for over one-half century for the management of menopausal symptoms, including vulvar and vaginal atrophy and vasomotor symptoms. Since the early 1980s, estrogen has also been used to help prevent the loss of bone mineral density.

The use of estrogen alone (unopposed by progestin drugs) therapy in women who have a uterus is associated with an increased incidence of endometrial hyperplasia and adenocarcinoma of the endometrium. A regimen that combines a progestin drug with estrogen has been shown to

[1] This guidance was developed by the Division of Reproductive and Urologic Drug Products (DRUDP) in the Center for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA).

[2] Drugs for the prevention or treatment of osteoporosis are reviewed by the Division of Metabolic and Endocrine Drug Products, Office of New Drugs, CDER.

reduce the risk of estrogen-induced endometrial hyperplasia without compromising the positive effects of estrogen on vasomotor symptoms, vulvar and vaginal atrophy symptoms, or bone mineral density.

Although adding progestins to estrogens decreases the risk of endometrial hyperplasia in postmenopausal women, the addition of progestins to estrogen therapy may be associated with increases in the risk of a variety of serious adverse events, such as breast cancer, thromboembolic events, and myocardial infarction. Therefore, this guidance encourages sponsors to develop the lowest doses and exposures for both estrogens and progestins for indications sought, even though specific relationships between dose, exposure, and risk of adverse events may not be known. Sponsors are encouraged to investigate dosing schedules and drug delivery systems that can achieve efficacy with lowest possible exposures.

III. DRUG PRODUCTS CONTAINING ESTROGEN ALONE

A. Indications

There are two symptomatic indications for estrogen alone therapy.

1. Moderate to severe vasomotor symptoms associated with the menopause

Vasomotor symptoms in postmenopausal women are commonly known as *hot flushes or hot flashes*. The severity of vasomotor symptoms are defined clinically as follows:

Mild:	sensation of heat without sweating
Moderate:	sensation of heat with sweating, able to continue activity
Severe:	sensation of heat with sweating, causing cessation of activity

2. Moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause

Patient self-assessed symptoms of vulvar and vaginal atrophy include:

- Vaginal dryness (none, mild, moderate or severe)
- Vaginal and/or vulvar irritation/itching (none, mild, moderate or severe)
- Dysuria (none, mild, moderate or severe)
- Vaginal pain associated with sexual activity (none, mild, moderate or severe)
- Vaginal bleeding associated with sexual activity (presence vs. absence)

B. Study Considerations

The Agency recommends that prior to initiating phase 3 development, adequate dose ranging studies be conducted to identify the doses to be studied in the proof of efficacy studies. We recommend conducting one or more placebo-controlled trials to support efficacy of each indication in Section III.A. One adequately designed clinical trial to study both indications concurrently is possible. We recommend that studies be randomized, double-blinded and of 12-

week duration. In addition, we recommend that studies identify the lowest effective dose by including an ineffective dose as one of the doses evaluated.

If the drug product is considered to be a new molecular entity or poses an unexpected safety concern, two placebo-controlled phase 3 clinical trials are recommended to establish safety and efficacy.

C. Inclusion and Exclusion Criteria

We recommend that:

- Only postmenopausal women be included in studies. We define *postmenopausal* as 12 months of spontaneous amenorrhea or 6 months of spontaneous amenorrhea with serum FSH levels > 40 mIU/ml or 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy.
- For the indication of treatment of moderate to severe vasomotor symptoms, study participants be enrolled who have a minimum of 7 to 8 moderate to severe hot flushes per day, or 50 to 60 per week at baseline.
- For the indication of treatment of moderate to severe symptoms of vulvar and vaginal atrophy, study participants be enrolled who have self-identified at least one moderate to severe symptom (see Section III.A.2) that is the most bothersome to her, have no greater than 5 percent superficial cells on a vaginal smear, and have a vaginal pH > 5.0.
- Study participants not be taking estrogen alone or estrogen/progestin containing drug products. The following washout periods are recommended before baseline assessments are made for subjects previously on estrogen alone or estrogen/progestin containing products:
  - — 1 week or longer for prior vaginal hormonal products (rings, creams, gels)
  - — 4 weeks or longer for prior transdermal estrogen alone or estrogen/progestin products
  - — 8 weeks or longer for prior oral estrogen and/or progestin therapy
  - — 8 weeks or longer for prior intrauterine progestin therapy
  - — 3 months or longer for prior progestin implants and estrogen alone injectable drug therapy
  - — 6 months or longer for prior estrogen pellet therapy or progestin injectable drug therapy
- Women >40 years have documentation of a negative screening mammogram (obtained at screening or within 9 months of study enrollment) and normal clinical breast examination prior to enrollment in clinical studies. Findings indicating any suspicion of breast malignancy would result in exclusion from enrollment.
- All subjects who have a uterus have endometrial biopsy performed at screening. Findings indicating endometrial hyperplasia or cancer would result in exclusion from enrollment.

D. Monitoring

We recommend that:

- All subjects who have a uterus undergo an endometrial biopsy at end-of-study.
- Any new findings noted during the conduct of the study or during the end-of-study physical examination (including findings related to the breast) receive careful and appropriate evaluation and be monitored until there is complete clinical resolution of any diagnosed condition.
- Sponsors provide plans for monitoring and/or reducing the risk of adverse endometrial effects in women who have a uterus.
- Safety assessments of lipids and of carbohydrate and coagulation parameters (antithrombin III, factor V Leiden, protein-C and protein-S) be conducted.
- Serum levels of the parent compounds and metabolites be measured.

E. Primary Endpoints

For the treatment of moderate to severe vasomotor symptoms, we recommend the following co-primary endpoints:

- Mean change in frequency of moderate to severe vasomotor symptoms from baseline to week 4
- Mean change in frequency of moderate to severe vasomotor symptoms from baseline to week 12
- Mean change in severity of moderate to severe vasomotor symptoms from baseline to week 4
- Mean change in severity of moderate to severe vasomotor symptoms from baseline to week 12

For the treatment of moderate to severe symptoms of vulvar and vaginal atrophy, we recommend the following co-primary endpoints.

- Mean change from baseline to week 12 in the moderate to severe symptom that has been identified by the patient as being the most bothersome to her
- Mean change from baseline to week 12 in vaginal pH
- Mean change from baseline to week 12 in vaginal maturation index (parabasal and superficial cells)

F. Study Analysis

For estrogen alone products intended to treat moderate to severe vasomotor symptoms, we recommend that the primary efficacy analyses show a clinically and a statistically significant

reduction, within 4 weeks of initiation of treatment and maintained throughout 12 weeks of treatment, in both the frequency and severity of hot flushes in the treated groups compared with the control groups. Subjective measures (e.g., daily patient diary entries) can be used as primary efficacy endpoints. Alternatively, objective measures (e.g., thermography) can be used both as primary efficacy endpoints and as validation of subjective endpoints. We recommend that study results clearly identify the lowest effective dose of estrogen to support the indication by demonstrating an ineffective lower dose.

For estrogen alone drug products intended to treat moderate to severe symptoms of vulvar and vaginal atrophy, we recommend that the primary efficacy analyses demonstrate a statistically significant improvement versus placebo from baseline to week 12 of treatment in all three of the following parameters:

1. Maturation Index (decrease of parabasal vaginal cells and increase in superficial vaginal cells)
2. Lowering of the vaginal pH
3. The moderate to severe symptom identified by the subject as being most bothersome to her

IV. DRUG PRODUCTS CONTAINING ESTROGEN PLUS PROGESTIN

The approval of specific fixed dose estrogen/progestin drug products for estrogen class labeling indications in women who have a uterus will be based on two criteria: (1) that each component contribute to the efficacy and safety as defined in the combination drug policy (see 21 CFR 300.50) and (2) the determination that a combination drug contains the lowest effective dose of each of its active components for their respective labeled indications.

A. Indications

1. Estrogen Component

The symptomatic indications for estrogen/progestin therapy are the same as those previously discussed under Section III.A of this guidance.

2. Progestin Component

The progestin component is added to estrogen alone regimens for safety purposes to oppose the adverse effects of estrogen on the endometrium in women who have a uterus. We recommend that sponsors propose low-dose combination estrogen/progestin regimens and dosing schedules that demonstrate endometrial safety and have acceptable endometrial bleeding profiles.

B. Study Considerations

To support the indication of the treatment of moderate to severe vasomotor symptoms or the treatment of moderate to severe symptoms of vulvar and vaginal atrophy, see Section III.B in this guidance.

To demonstrate protection of the endometrium, we recommend that a single, 12-month, randomized, double-blind, dose-ranging phase 3 clinical trial be conducted and include two or more progestin drug treatment arms for each estrogen dose studied. However, the indications in Section III.A can be studied as part of the 12-month endometrial protection study, provided all entrance criteria for each indication are met and the study is powered adequately for each endpoint. We recommend that study results clearly identify the lowest effective dose of estrogen (as described in Section III.B) and the lowest effective dose of progestin to support endometrial safety by demonstrating an ineffective lower dose on the endometrium.

If the drug to be studied is considered to be a new molecular entity or if it poses unique safety concerns, two placebo-controlled phase 3 clinical trials are recommended to establish safety and efficacy.

C. Inclusion and Exclusion Criteria

Please refer to the criteria set out in Section III.C., except as specified below.

We recommend that:

- All subjects have a uterus and have an evaluable screening endometrial biopsy (i.e., endometrial tissue sufficient for diagnosis). Findings indicating endometrial hyperplasia or cancer would result in exclusion from enrollment and subjects would be referred for *standard of care* clinical management.
- A negative screening mammogram (obtained at screening or within 3 months of study enrollment) and normal clinical breast examination be documented prior to enrollment in clinical studies for women > 40 years old. Findings indicating any suspicion of breast malignancy would result in exclusion from enrollment.

D. Monitoring

We recommend that:

- The endometrial tissue obtained by endometrial biopsy at screening, during the conduct of the study, and at the end-of-study be processed in the same manner by a central laboratory.
- Endometrial biopsies and not uterine ultrasounds be used for the evaluation of endometrial hyperplasia (sponsors interested in establishing a correlation between transvaginal ultrasound and endometrial biopsy results may perform transvaginal ultrasound immediately preceding endometrial biopsies).
- A single pathologist reader (any one of the three blinded pathologists) initially assess the slides from the endometrial biopsies obtained at screening or because of participant bleeding while on study drug (safety reading).

- For the efficacy evaluation, three independent expert pathologists, blinded to treatment group and to each other's readings, determine the diagnosis for endometrial biopsy slides during the conduct of the study.
- Curricula vitae for participating pathologists be provided to the FDA and document expertise in gynecologic pathology.
- Participating study pathologists be from different institutions with independent fiduciary and organizational reporting, and these pathologists not meet to review slides before or during the conduct of the clinical trial.
- Standardized criteria as provided in Blaustein's pathology text (Pathology of the Female Genital Tract) be used for the diagnosis of endometrial hyperplasia (see Appendix for recommended histologic characteristics of the endometrium).
- Endometrial polyps be fully characterized as to the glandular proliferation and atypia (see Appendix for additional histologic characteristics of the specimen).
- Subjects found to have endometrial hyperplasia or adenocarcinoma of the endometrium be excluded from further drug treatment (if discovered during study drug treatment period) and referred for *standard of care* clinical management and followed to complete resolution, and the report of any medical or surgical procedures and the resultant pathology be provided to the FDA.
- If hyperplasia is diagnosed by the single safety reader for a subject who has bled while on study drug, this diagnosis be maintained for the efficacy evaluation and the slides become part of the slide set given to the two other pathologists for reading.
- For the efficacy evaluation, the concurrence of two of the three pathologists be accepted as the final diagnosis. If there is no agreement among the three pathologists, the most severe pathologic diagnosis (i.e., atypical hyperplasia > complex hyperplasia > simple hyperplasia > benign endometrium) would be used as the final diagnosis.
- The slide set distributed to each of the three pathologists for the end-of-study pathology review incorporate control sides representing a randomly selected 10 percent of the screening normal slides and all slides from subjects excluded for the diagnosis of hyperplasia or cancer to insure quality control.
- Digital recording of diagnostic areas of the slides be maintained by the central laboratory and be made available upon FDA request.
- Any new findings noted during the conduct of the study and on end-of-study physical examination (including findings related to the breast) receive careful and appropriate evaluation and be monitored until there is complete clinical resolution of any diagnosed condition.
- Safety assessments of lipids and of carbohydrate and coagulation parameters (antithrombin III, factor V Leiden, protein-C and protein-S) be conducted.
- Serum levels of the parent compounds and metabolites be measured.

E. Primary Endpoints

For protection of the endometrium, we recommend the evaluation of the incidence rate of endometrial hyperplasia at 12 months.

F. Study Analysis

See Section III.F. for analysis of primary endpoints for treatment of moderate or severe vasomotor symptoms or moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. The objective of the clinical trial is to demonstrate the lowest effective dose of the progestin drug that reduces the estimated risk of endometrial hyperplasia after 1 year of estrogen/progestin treatment. The reported 1-year background incidence rate for endometrial hyperplasia in postmenopausal women and in postmenopausal women treated with currently marketed combination estrogen/progestin drugs is approximately 0-1 percent. We recommend that the results from the clinical trial demonstrate a hyperplasia rate that is ≤ 1 percent with an upper bound of the one-sided 95 percent confidence interval for that rate that does not exceed 4 percent. The frequency of atypical hyperplasia and cancer are important additional factors to be considered in determining approvability of the drug product. The incidence of hyperplastic polyps and associated atypia would be considered in the safety review.

APPENDIX: HISTOLOGIC DESCRIPTIONS RECOMMENDED FOR USE WHEN READING ENDOMETRIAL BIOPSY SLIDES

Histologic Characteristics of the Endometrium

0. No tissue

1. Tissue insufficient for diagnosis

2. Atrophic

3. Inactive

4. Proliferative

    a. Weakly proliferative

    b. Active proliferative

    c. Disordered proliferative

5. Secretory

    a. Cyclic type

    b. Progestational type (including stromal decidualization)

6. Menstrual type

7. Simple hyperplasia without atypia

8. Simple hyperplasia with atypia

9. Complex hyperplasia without atypia

10. Complex hyperplasia with atypia

11. Carcinoma (specify type)

Additional Histologic Characteristics

If there are any polyps, please specify the type or types.

- Functional
- Atrophic
- Hyperplastic without atypia
- Hyperplastic with atypia
- Carcinomatous

If there is any stromal tissue, please specify the type or types.

- Smooth muscle tissue, normal
- Features suggestive of adenomyoma
- Features suggestive of stromal nodule
- Sarcoma (specify type)

If there is any metaplasia, please specify the type or types.

- Squamous
- Papillary
- Eosinophilic
- Ciliated
- Mucinous
- Syncytial
- Other type (specify type)

If there is any cervical tissue, please specify the type or types.

- Fragments of negative cervical epithelium
- Endocervical polyp
- Atypical endocervical glandular epithelium
- Atypical squamous metaplasia
- Squamous dysplasia
- Cervical carcinoma

Table 2: Schedule of evaluations

Study Schedule	Screening Period	Run-in Visit	Run-in Period	End Of Run-in	Baseline	Double-blind Treatment Period								Post Treatment
Duration	Up to 7 days	1 day	12 days	1 day	1 day	85 days								1 day
Visit Name	Screening	Run-in		End Of Run-in	Baseline[g]	Day 1 to 84	Day 7	Day 14	Day 21	Day 28	Day 42	Day 56	End Of Study Day 85[h]	7 Days After Last Dose
Week								2		4			12	
Visit Window			+ 3 days				+ 3 days	+ 3 days	+ 3 days	+ 3 days	+ 3 days	+ 3 days	+ 3 days	± 3 days
Clinic Visit	Yes	Yes		Yes	Yes			Yes		Yes			Yes	
Telephone Visit							Yes		Yes		Yes	Yes		Yes
Informed Consent	X													
Review of Inclusion/Exclusion Criteria	X													
Hot Flash Eligibility Criteria (IVRS/IWRS)	X				X									
Medical and Psychiatric History	X													
Physical Examination	X												X	
Vital Signs[a]	X				X			X		X			X	
Weight and Height[b]	X				X			X		X			X	
Electrocardiogram	X												X	
Hematology[c]	X												X	
Chem 20[d]	X												X	
FSH	X													
Urine Drug Screen	X													
Urine Pregnancy Test (all females who are not at least 2 years postmenopausal)		X			X			X		X			X	
Record Concomitant Therapies	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record Adverse Events[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 2: Schedule of evaluations (Continued)

Study Schedule	Screening Period	Run-in Visit	Run-in Period	End Of Run-in	Baseline	Double-blind Treatment Period								Post Treatment
Duration	Up to 7 days	1 day	12 days	1 day	1 day	85 days								1 day
Visit Name	Screening	Run-in		End Of Run-in	Baseline[a]	Day 1 to 84	Day 7	Day 14	Day 21	Day 28	Day 42	Day 56	End Of Study Day 85[b]	7 Days After Last Dose
Week								2		4			12	
Visit Window			+3 days				+3 days	+3 days	+3 days	+3 days	+3 days	+3 days	+3 days	±3 days
Clinic Visit	Yes	Yes		Yes	Yes			Yes		Yes			Yes	
Telephone Visit							Yes		Yes		Yes	Yes		Yes
Randomization					X									
Dispense Study Drug		X			X Month 1					X Month 2 and 3				
Subject Self-administration of Study Drug (once daily at bedtime)			X			X								
Collect Study Drug				X						X			X	
Perform Drug Accountability				X				X		X			X	
Subject Completion of Hot Flash Diary (IVRS/IWRS)			X (daily)			X (daily)								
Subject Completion of Sleep Diary (IVRS/IWRS)			X (daily)			X (daily)								
Subject Completion of Symptom Assessment Questionnaires (IWRS)					X					X			X	
PGI (eCRF)										X			X	
CGI (eCRF)					X					X			X	
C-SSRS (eCRF)					X			X		X			X	
Subject Completion of DESS scale (IWRS)														X

[a] To include systolic and diastolic blood pressure, heart rate and body temperature.

[b] Weight and height were determined at Screening; weight was also determined at Baseline and on Days 28 and 85 (or early discontinuation).
[c] Hematology included hemoglobin, hematocrit, platelets, total white blood cell count, neutrophils %, lymphocytes %, and eosinophils %.
[d] Chem 20 panel included sodium, potassium, chloride, total carbon dioxide (bicarbonate), creatinine, glucose, urea nitrogen, albumin, total calcium, total magnesium, phosphorus, alkaline phosphatase, alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin, direct bilirubin, lactate dehydrogenase, total protein, total creatine kinase, and uric acid.
[e] AE monitoring to continue throughout the duration of the study, beginning from the time of informed consent signing up to 7 days following the last dose of study medication.
[f] Included the Hospital Anxiety and Depression Scale (HADS), Profile of Mood States (POMS), Greene Climacteric Scale (GCS), Hot Flash Related Daily Interference Scale (HFRDIS), Arizona Sexual Experience Scale (ASEX), Numerical Rating Scale (NRS), and Patient Satisfaction Questionnaire (PSQ; only at Day 28 and Day 85).
[g] For all eligible subjects who was randomized. Subjects who did not meet hot flash eligibility criteria (ie, do not have more than 7–8 moderate to severe hot flashes per day (average) or 50–60 hot flashes per week) or did not have at least 9 days of diary data or missed 3 or more doses of study drug was discontinued.
[h] Or early discontinuation.

CGI=Clinical Global Impression; C-SSRS=Columbia Suicide Severity Rating Scale; DESS=discontinuation-emergent signs and symptoms; eCRF=electronic case report form; FSH=follicle stimulating hormone; PGI=Patient Global Improvement; IVRS=Interactive Voice Response System; IWRS=Interactive Web Response System.

Table 3: Schedule of evaluations

Study Schedule	Screening Period	Run-in Visit	Run-in Period	End of Run-in	Baseline	Double-blind Treatment Period											Post-treatment
Duration	Up to 7 days	1 day	12 days	1 day	1 day	169 days											1 day
Visit Name	Screening	Run-In		End of Run-in	Baseline[g]	1 to 168	Day 7	Day 14	Day 21	Day 28	Day 42	Day 56	Day 84	Day 112	Day 140	End of Study Day 169[h]	7 days After Last Dose
Week								Week 2		Week 4			Week 12			Week 24	
Visit Window			+3 days				+3 days	+3 days	+3 days	+3 days	+3 days	+3 days	+3 days	+3 days	+3 days	+3 days	±3 days
Clinic Visit	Yes	Yes		Yes	Yes			Yes		Yes			Yes			Yes	
Telephone Visit							Yes		Yes		Yes	Yes		Yes	Yes		Yes
Informed Consent	X																
Review of Inclusion/Exclusion Criteria	X																
Medical and Psychiatric History	X																
Hot Flash Eligibility Criteria (IVRS/IWRS)	X				X												
Physical Examination	X															X	
Vital Signs[a]	X				X			X		X			X			X	
Weight and Height[b]	X				X			X		X			X			X	
ECG	X															X	
Hematology[c]	X															X	
Chem 20[d]	X															X	
FSH	X																
Urine Drug Screen	X																

Table 3: Schedule of evaluations (Continued)

Study Schedule	Screening Period	Run-in Visit	Run-in Period	End of Run-in	Baseline	Double-blind Treatment Period											Post-treatment
Urine Pregnancy Test (all females who are not at least 2 years postmenopausal)		X			X			X		X			X			X	
Record Concomitant Therapies	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record AEs[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization					X												
Dispense Study Drug		X			X Month 1					X Month 2 and 3			X Month 4, 5, and 6				
Subject Self-administration of Study Drug (once daily at bedtime)			X			X											
Collect Study Drug				X						X			X			X	
Perform Drug Accountability				X				X		X			X			X	
Subject Completion of Hot Flash Diary*			X (daily)			X (daily)											
Subject Completion of Sleep Diary*			X (daily)			X (daily)											
Subject Completion of Symptom Assessment Questionnaires§					X					X			X			X	
Investigator Completion of CGI (eCRF)					X					X			X			X	
Subject Completion of STS§					X			X		X			X			X	

Table 3: Schedule of evaluations (Continued)

Study Schedule	Screening Period	Run-in Visit	Run-in Period	End of Run-in	Baseline	Double-blind Treatment Period											Post-treatment
Subject Completion of DESS scale§																	X

[a] To include systolic and diastolic blood pressure, heart rate, and body temperature
[b] Weight and height will be determined at Screening; weight will only be determined at Baseline and on Days 28, 84, and 169 (or early discontinuation).
[c] Hematology to include hemoglobin, hematocrit, platelets, total white blood cell count, neutrophils %, lymphocytes %, and eosinophils %.
[d] Chem 20 panel includes sodium, potassium, chloride, total carbon dioxide (bicarbonate), creatinine, glucose, urea nitrogen, albumin, total calcium, total magnesium, phosphorus, alkaline phosphatase, ALT, AST, total bilirubin, direct bilirubin, lactate dehydrogenase, total protein, total creatine kinase, and uric acid. FSH only at Screening.
[e] AE monitoring to continue throughout the duration of the study, beginning from the time of informed consent signing up to 7 days following the last dose of study medication.
[f] To include HADS, POMS, GCS, HFRDIS, ASEX, and NRS
[g] For all eligible subjects who will be randomized. Subjects who do not meet hot flash eligibility criteria (ie, do not have more than 7 to 8 moderate to severe hot flashes per day [average] or 50 to 60 moderate to severe hot flashes per week) or did not have at least 9 days of diary data or missed 3 or more doses of study drug will be discontinued.
[h] Or early discontinuation

*Completed using the IVRS/IWRS, §Completed using the IWRS.
AE=adverse event; ALT=alanine transaminase; ASEX=Arizona Sexual Experience Scale; AST=aspartate transaminase; CGI=Clinical Global Impression; DESS=Discontinuation Emergent Signs and Symptoms; ECG=electrocardiogram; eCRF=electronic case report form; FSH=follicle-stimulating hormone; GCS=Greene Climacteric Scale; HADS=Hospital Anxiety and Depression Scale; HFRDIS=Hot Flash Related Daily Interference Scale; IVRS=Interactive Voice Response System; IWRS=Interactive Web Response System; NRS=Numerical Rating Scale; POMS=Profile of Mood States.